

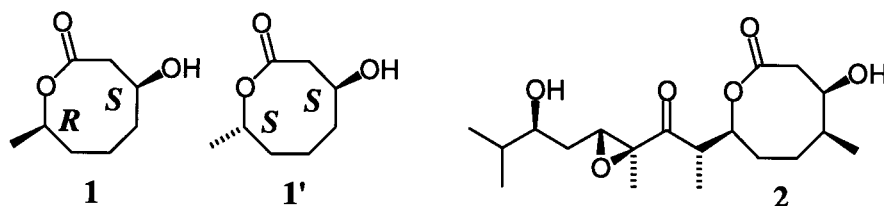
STEREOSELECTIVE TOTAL SYNTHESIS OF CEPHALOSPOROLIDE D[#]

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Abstract — An efficient method for the synthesis of (-)-cephalosporolide D is established *via* successive enantioselective aldol and effective 8-membered ring lactone forming reactions.

Cephalosporolide D (**1** or **1'**), a metabolite of fungus, was isolated in 1985 from the *Cephalosporium aphidicola* together with related compounds by Hanson *et al.*¹ The structure containing two chiral centers and an unusual saturated 8-membered ring lactone was determined by MS spectra, IR absorption, ¹H and ¹³C NMR spectral 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 and absolute stereochemistries have not determined to date. The similar characteristic structure was also found in octalactin A (**2**) which exhibited a potent cytotoxic activity against some tumor cell lines.² In this paper, determination of stereochemistry of cephalosporolide D and its asymmetric synthesis by way of enantioselective aldol and recently developed lactonization reactions are described in detail.³

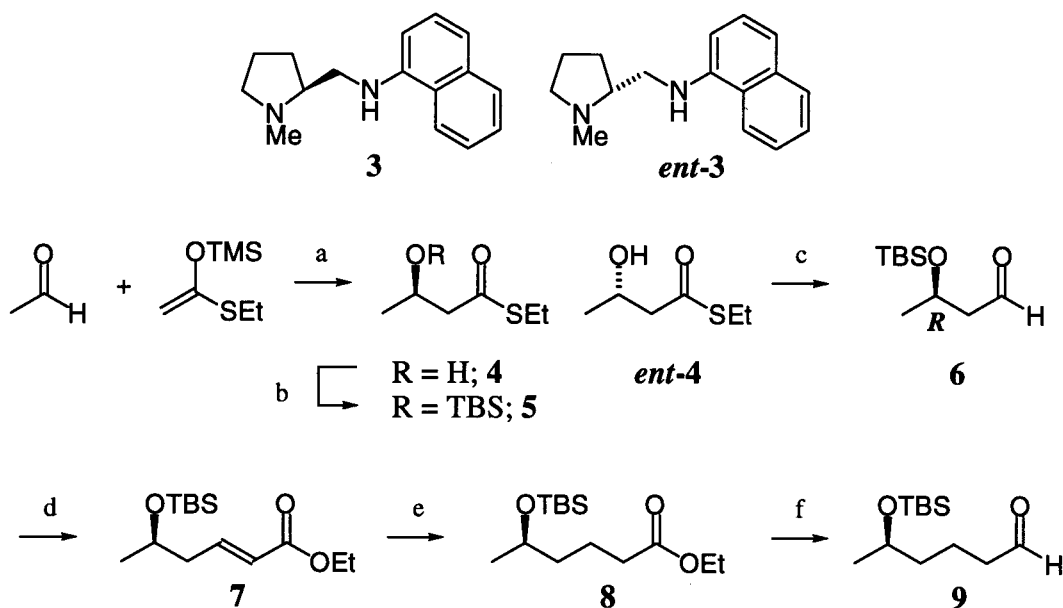


Scheme 1.

Optically active *S*-ethyl (*R*)-3-hydroxybutanal (**4**) or its enantiomer (*ent*-**4**) were respectively synthesized with high enantioselectivities by asymmetric aldol reaction between acetaldehyde and enol silyl ether derived from *S*-ethyl ethanethioate using chiral Lewis acid consisted of Sn(OTf)₂, chiral diamine (**3**) (or *ent*-**3**) and *n*Bu₃SnF.⁴

[#] The authors dedicate this paper to Professor Teruaki Mukaiyama on the celebration of his 73rd birthday.

The aldol (**4**) was converted to optically active 3-(*tert*-butyldimethylsiloxy)butanal (**6**) in good yield after protection with a combination of TBSOTf and 2,6-lutidine and subsequent reduction with DIBAL. Absolute configuration of **6** was determined by comparing of its optical rotation with that in literature.⁵ Horner-Wadsworth-Emmons reaction of aldehyde (**6**) with (EtO)₂POCH₂COOEt produced *trans*-unsaturated ester (**7**) in high yield and it was in turn transformed to the corresponding saturated siloxy aldehyde (**9**) by successive hydrogenation under hydrogen atmosphere in the presence of palladium on carbon and reduction with DIBAL.



a) Sn(OTf)₂, ⁿBu₃SnF, chiral diamine (**3**), CH₂Cl₂, -95 °C (78%, 96% ee for **4**); Sn(OTf)₂, ⁿBu₃SnF, chiral diamine (*ent-3*), CH₂Cl₂, -95 °C (83%, 96% ee for *ent-4*); b) TBSOTf, 2,6-lutidine, CH₂Cl₂, 0 °C (96%); c) DIBAL, toluene, -78 °C (84%); d) (EtO)₂POCH₂COOEt, NaH, THF, 0 °C (83%); e) H₂, 10% Pd/C, EtOH, rt (95%); f) DIBAL, toluene, -78 °C (90%).

Scheme 2.

The reaction of the chiral aldehyde (**9**) with lithium enolate derived from *S*-ethyl ethanethioate gave the isomeric aldols (**10**) and (**10'**) with poor diastereoselectivity (**10** / **10'** = 47 / 53). However, the asymmetric aldol reaction between aldehyde (**9**) and the above enol silyl ether in the presence of the chiral Lewis acid consisted of Sn(OTf)₂, chiral diamine (*ent-3*) and ⁿBu₃SnF under standard reaction conditions produced the corresponding aldol (**10**) in good yield with high stereoselectivity (**10** / **10'** = 97 / 3). Further, diastereoisomeric aldol (**10'**) was also prepared by the same asymmetric aldol reaction using chiral diamine (**3**) with high stereoselectivity (**10** / **10'** = 3 / 97). The stereochemistry at C-3 was not yet clear at this stage; however, the empirical rule of our asymmetric aldol reaction made us assume that aldol (**10**) and (**10'**) would have (3*S*,7*R*) and (3*R*,7*R*) configurations, respectively.⁴ When the aldol reaction of aldehyde (**9**) with the enol silyl ether was tried in the presence of a catalytic amount of SnCl₄, a

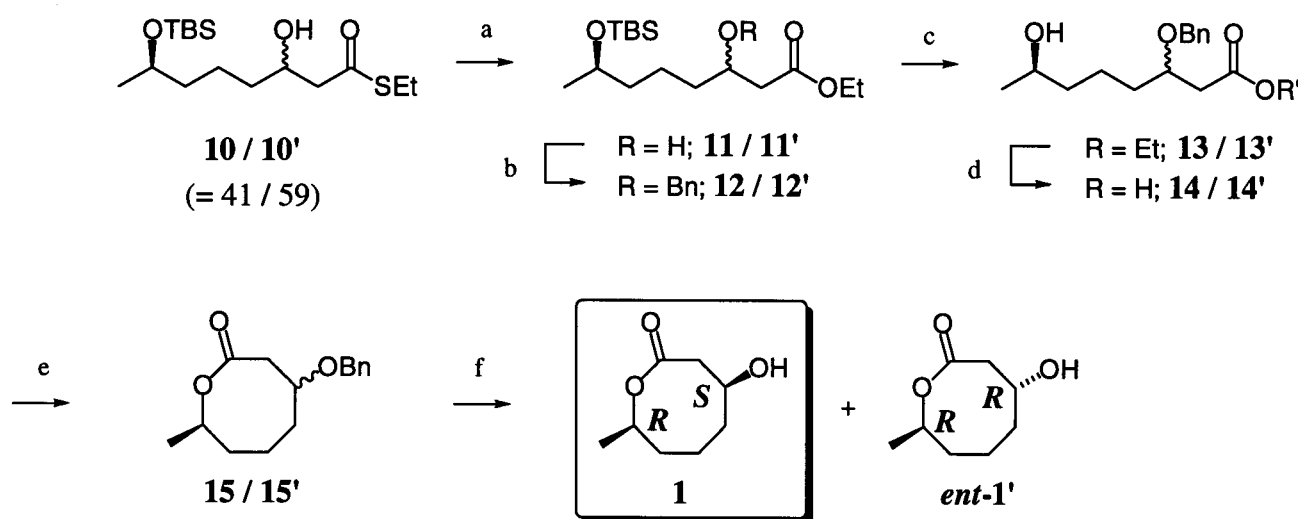
diastereomeric mixture of the aldols was obtained in good yield with moderate stereoselectivity (**10** / **10'** = 41 / 59).

Table 1. Synthesis of aldols (**10**) and (**10'**) by asymmetric aldol reaction.

Promoter	Yield / %	10 / 10'	Promoter	Yield / %	10 / 10'
BF ₃ ·OEt ₂	45	47 / 53	Sn(OTf) ₂ , <i>n</i> Bu ₃ SnF, <i>ent</i> -3	89	97 / 3
AlCl ₃	62	44 / 56			
SnCl ₄	62	41 / 59	Sn(OTf) ₂ , <i>n</i> Bu ₃ SnF, 3	62	3 / 97
Sn(OTf) ₂	44	50 / 50			

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 (**10**) or (**10'**). Protection of hydroxyl groups of **10** and **10'** 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 (**10**) and (**10'**) were converted to the corresponding esters (**11**) and (**11'**) by transesterification in the presence of Ag(OCOCF₃) and *i*Pr₂NEt in EtOH. Benzylation of the esters (**11**) and (**11'**) using trichloromethyl benzylimidate proceeded rapidly to afford a mixture of the desired dialkoxy esters (**12**) and (**12'**) in high yield as expected. *tert*-Butyldimethylsilyl groups of **12** and **12'** were removed on treatment with acetic acid and water in THF, then saponification of a mixture of thus formed esters (**13**) and (**13'**) with aqueous KOH afforded a mixture of the desired hydroxy carboxylic acids (**14**) and (**14'**) in good yield. Then, lactonization of the mixture of **14** and **14'** was tried by previously reported mixed anhydride method using a catalytic amount of Lewis acids and a stoichiometric amount of *p*-trifluoromethylbenzoic anhydride.^{6a-d} When the reaction was carried out in the presence of a catalytic amount of TiCl₂(OTf)₂, a mixture of 8-membered ring lactones (**15**) and (**15'**) was obtained only in 2% yield. On the other hand, the cyclization reaction catalyzed by Sc(OTf)₃ gave a mixture of 8-membered ring lactones (**15**) and (**15'**) in 44% yield, and 31% of the mixture of **14** and **14'** was

recovered.^{6e,f} After screening several catalysts in this reaction, it was found that $\text{Hf}(\text{OTf})_4$ promoted the cyclization effectively to produce a mixture of desired 8-membered ring lactones (**15**) and (**15'**) in 67% yield, and 17% of the mixture of **14** and **14'** was recovered.⁷ 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.⁸ 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 (**15**) and (**15'**) was obtained in 74% yield although the hydroxy carboxylic acids (**14**) and (**14'**) were not recovered.⁹ Lactonization of the precursors by activation using 2-chloro-1-methylpyridinium iodide with triethylamine¹⁰ or di-2-pyridyldisulfide with triphenylphosphine¹¹ also afforded a mixture of desired lactones in 64% or 34% yield, respectively. Debenzylation of lactones (**15**) and (**15'**) took place smoothly to yield a mixture of lactones (**1**) and (**ent-1'**) in the ratio of 41 to 59.



a) $\text{Ag}(\text{OCOCF}_3)$, $i\text{Pr}_2\text{NEt}$, EtOH, rt (100%); b) $\text{BnOC}(\text{CCl}_3)=\text{NH}$, TfOH, CH_2Cl_2 , rt (98% of **12/12'**, 1% of **13/13'**); c) AcOH, H_2O , THF, rt (100%); d) KOH, H_2O , MeOH, rt (61%); e) $\text{Hf}(\text{OTf})_4$, ($p\text{-CF}_3\text{C}_6\text{H}_4\text{CO}$)₂O, MeCN, THF, reflux (2.34 mM, slow addition over a 15 h period, 81% based on 83% conversion); f) H_2 , 10% Pd/C, EtOH, rt (98%, **1/ent-1'** = 41/59).

Scheme 3.

As shown in Figure 1, ^1H NMR spectra of thus obtained mixture of lactones (**1**) and (**ent-1'**) showed that naturally occurring cephalospoloride D (**1**, $J_{2-3} = 5.6, 3.6$ Hz) is a minor stereoisomer, which is assumed to be in (3*S*,7*R*) configuration, while the 3-epicephalospoloride D (**ent-1'**, $J_{2-3} = 9.6, 5.8$ Hz) is a major stereoisomer, which is assumed to be in (3*R*,7*R*) configuration.

Conformational search with PM3 semi empirical molecular orbital calculation including solvent effect (hexadecane or water) of lactones (**1**) and (**ent-1'**) showed that these compounds have depicted structures in solvent (Figure 2).¹² It was shown that lactone (**1**) has two stable conformations (ΔH_{rxn} (gas) = 1.21 kcal/mol, ΔH_{rxn} (hexadecane) = 1.32 kcal/mol, ΔH_{rxn} (H_2O) = 1.22 kcal/mol) and stereochemical correlations among atoms at H(2)-C(2)-C(3)-H(3) of each conformer are synclinal / synclinal.

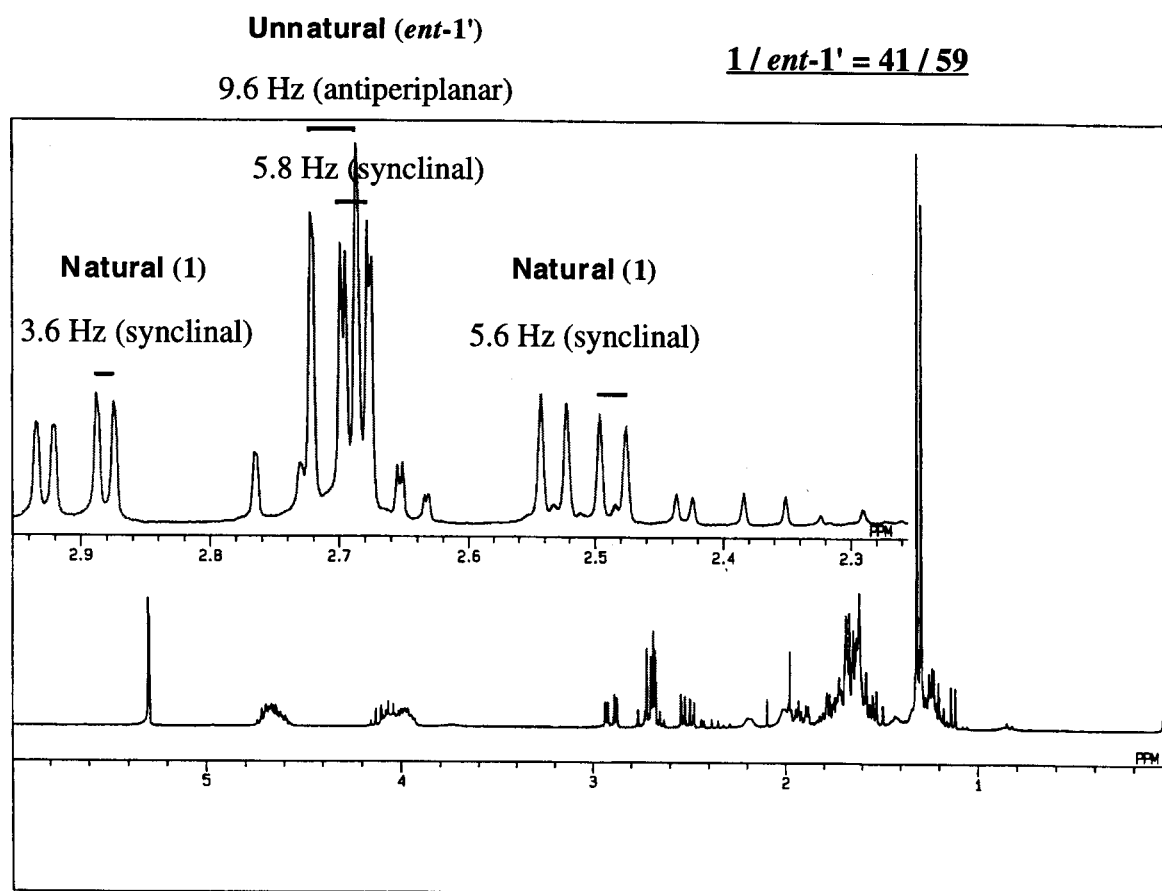


Figure 1. NMR spectra of the mixture of lactones (**1**) and (*ent*-1') in CD₂Cl₂.

Diastereomeric lactone (*ent*-1') has also two stable conformations (ΔH_{rxn} (gas) = 1.21 kcal/mol, ΔH_{rxn} (hexadecane) = 1.22 kcal/mol, ΔH_{rxn} (H₂O) = -0.27 kcal/mol), however, stereochemical correlations among atoms at H(2)-C(2)-C(3)-H(3) of each conformer are antiperiplanar / synclinal. By comparison of this structural data with coupling constants observed by their ¹H NMR, it is also suggested that the minor stereoisomer (natural form) has (3*S*,7*R*) configuration (**1**), whereas the major stereoisomer (unnatural form) has (3*R*,7*R*) configuration (*ent*-1').

Finally, (-)-cephalosporolide **D** (**1**) was synthesized from the aldol (**10**) by successive protection, deprotection and lactonization procedures. Though 16-membered ring diolide (**16**) was not produced by using our cyclization under concentrated reaction conditions, a very small amount of **16** was obtained along with the desired 8-membered ring lactone (**15**) when Yamaguchi's method was applied to carboxylic acid (**14**) under relatively concentrated reaction conditions.

The synthetic lactone (**1**) was recrystallized from hexane and optically and chemically pure lactone (**1**) was obtained ($[\alpha]_{\text{D}}^{28}$ -46.8° (c 2.40, CHCl₃)). The spectroscopic properties of synthetic crystalline sample including its optical rotation were identical with those of **1** reported by Hanson *et al.* ($[\alpha]_{\text{D}}^{20}$ -46.5° (c 2.23, CHCl₃)).¹ Furthermore, X-Ray crystallography of synthetic lactone (**1**) showed its exact relative stereochemistry and conformation.¹² Further, as shown in Figure 3, the lactone (**1**) has the second stable conformation estimated by calculation.

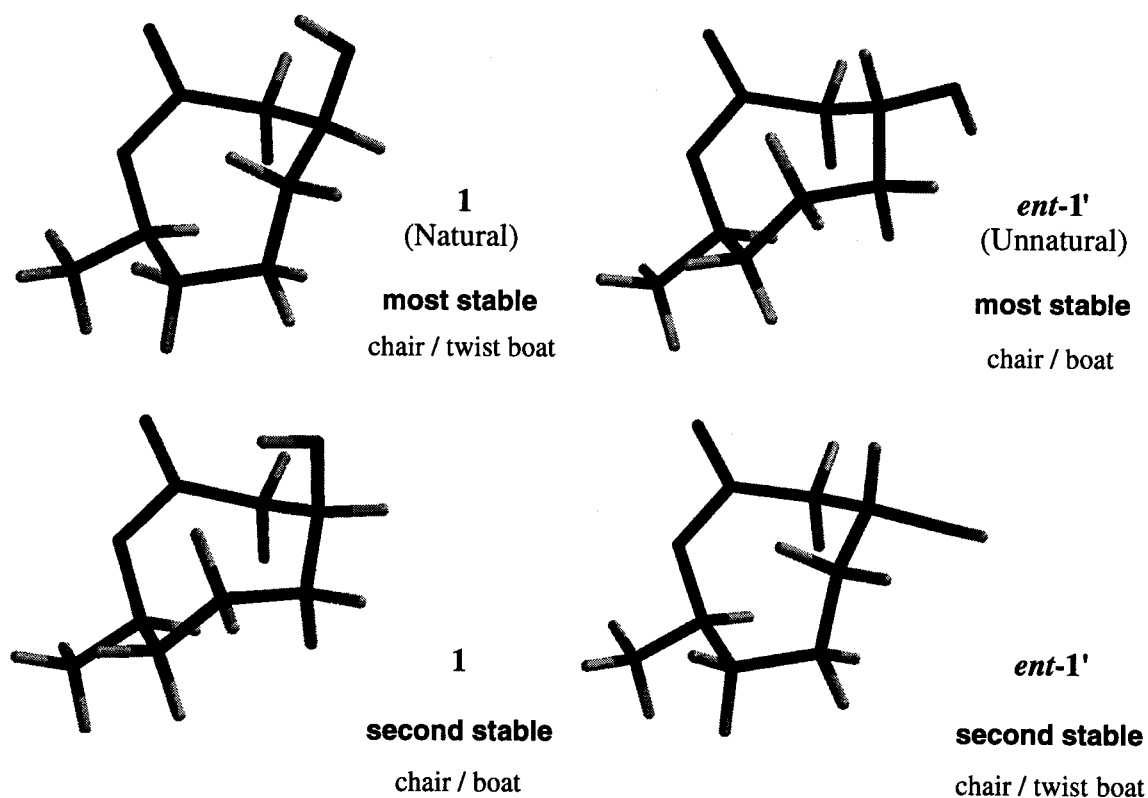
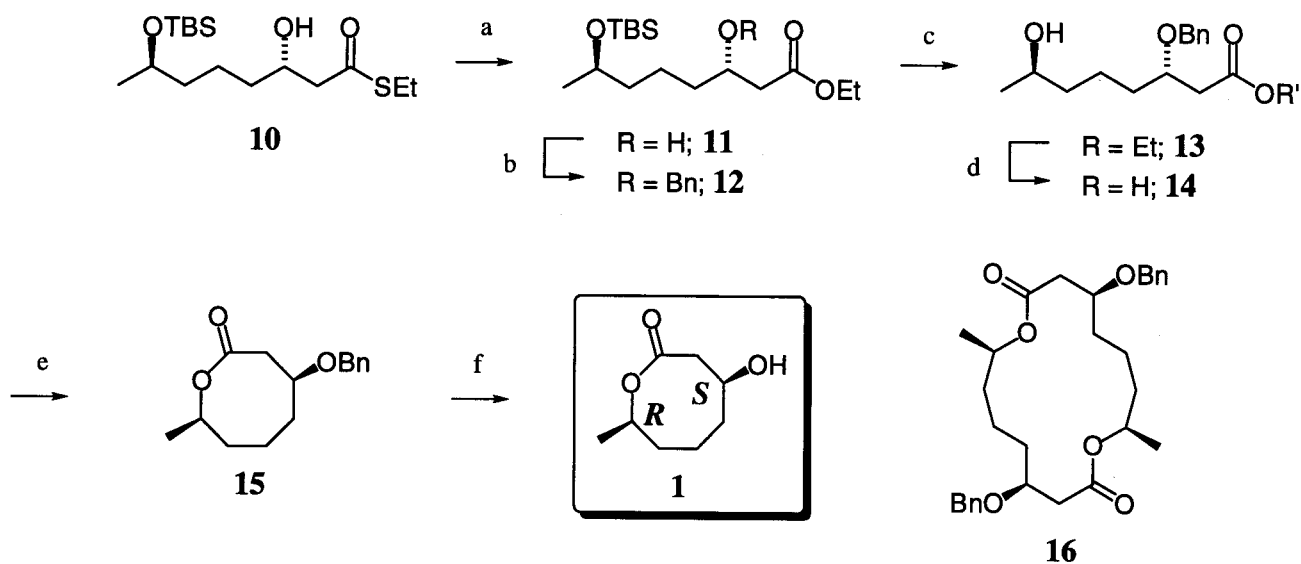


Figure 2. Stable conformations of lactones (**1**) and (*ent*-**1'**) calculated with PM3.



a) $\text{Ag}(\text{OCOCF}_3)$, $i\text{Pr}_2\text{NEt}$, EtOH , rt (93%); b) $\text{BnOC}(\text{CCl}_3)=\text{NH}$, TfOH , CH_2Cl_2 , rt (85% of **12**, 9% of **13**); c) AcOH , H_2O , THF , rt (95%); d) KOH , H_2O , MeOH , rt (67%); e) $\text{Hf}(\text{OTf})_4$, $(p\text{-CF}_3\text{C}_6\text{H}_4\text{CO})_2\text{O}$, MeCN , THF , reflux (1.66 mM, slow addition over a 8 h period, 77% based on 61% conversion); f) H_2 , 10% Pd/C , EtOH , rt (73% based on 90% conversion).

Scheme 4.

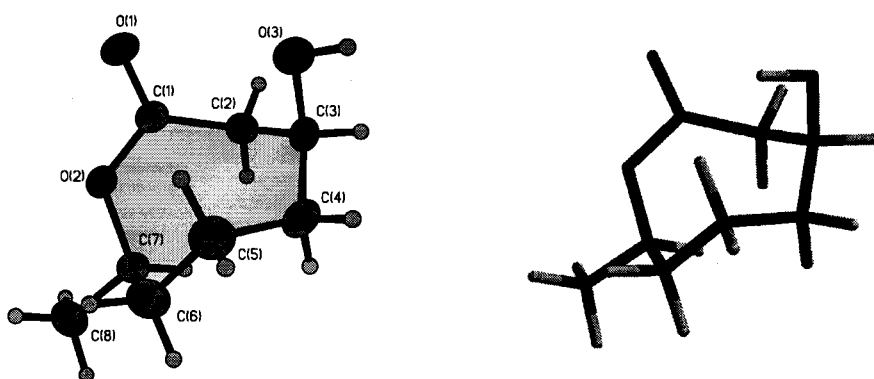


Figure 3. ORTEP drawing of lactone (**1**) and second stable conformation of **1** calculated with PM3.

It is assumed that there is conformational stabilization effect by hydrogen bonding between neighbor molecules in crystal packing structure as shown in Figure 4.

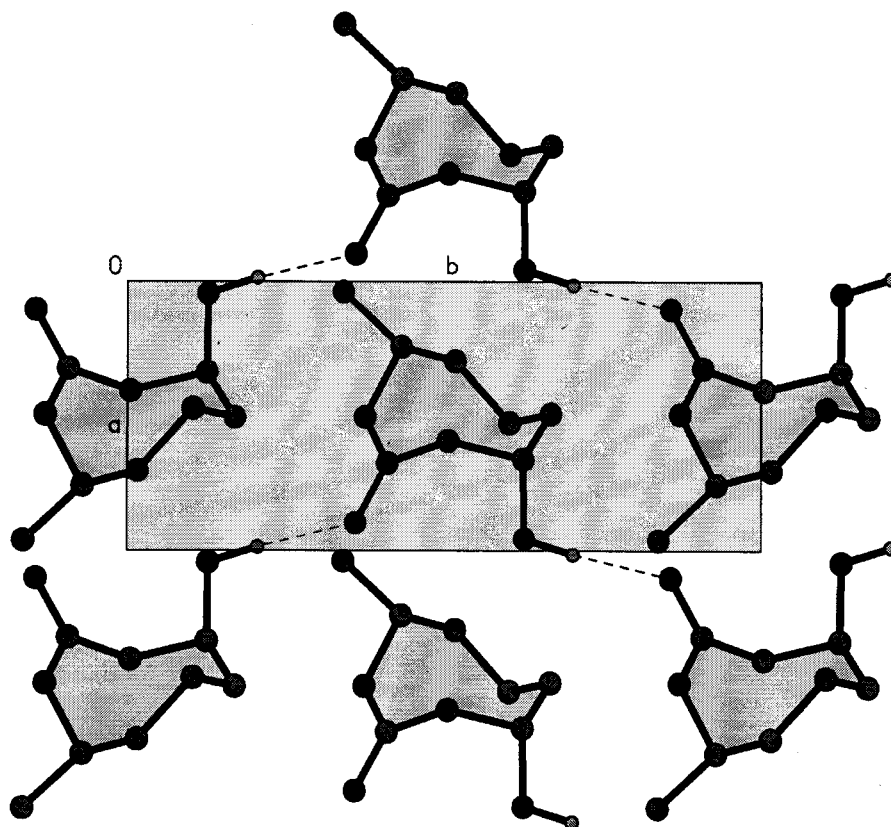


Figure 4. Crystal packing structure of cephalosporolide D (**1**).

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 configurations of the lactone (**1**) including its conformation were definitely determined by its enantioselective synthesis.

EXPERIMENTAL

General techniques: All melting points were measured on a Yanaco MP-S3 micro melting point apparatus. Optical rotations were recorded on a Jasco DIP-360 or a Jasco P-1020 digital polarimeter. IR spectra were recorded on a Horiba FT-300 infrared spectrophotometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270L, a JEOL ALPHA-500, a JEOL RAMBDA-500 or a Bruker AVANCE DPX-300 spectrometer with tetramethylsilane (TMS), chloroform (in chloroform- d), dichloromethane (in dichloromethane- d_2) or benzene (in benzene- d_6) as internal standard. HPLC was carried out using a Hitachi LC-Organizer, L-4000 UV Detector, L-6200 Intelligent Pump, and D-2500 Chromato-Integrator. High-resolution MS spectra were recorded on a JEOL JMS-SX102A instrument using 4-nitrobenzyl alcohol as a matrix. Column chromatography was performed on Silica gel 60 (Merck) or Wakogel B5F. Thin layer chromatography was performed on Wakogel B5F.

All reactions were carried out under argon atmosphere in dried glassware, unless otherwise noted. Dichloromethane was distilled from diphosphorus pentoxide, then calcium hydride, and dried over MS 4 Å, benzene and toluene were distilled from diphosphorus pentoxide, and dried over MS 4 Å, and THF and ether were distilled from sodium / benzophenone immediately prior to use. All reagents were purchased from Tokyo Kasei Kogyo Co., Ltd., Kanto Chemical Co., Inc. or Aldrich Chemical Co., Inc., and used without further purification unless otherwise noted.

S-Ethyl (*R*)-3-hydroxybutanoate (4):¹⁴ Chiral diamine (**3**) was prepared by a literature method.¹⁵ 1-Ethylthio-1-(trimethylsiloxy)ethene was prepared by a literature method.¹⁶ To a suspension of tin(II) trifluoromethanesulfonate (445 mg, 1.07 mmol) in dichloromethane (5 mL) at rt were added a solution of chiral diamine (**3**) (313 mg, 1.28 mmol) in dichloromethane (5 mL) and tributyltin fluoride (341 mg, 1.10 mmol). After the reaction mixture had been stirred for 10 min at -95 °C, a solution of 1-ethylthio-1-(trimethylsiloxy)ethene (132 mg, 0.747 mmol) in dichloromethane (2.5 mL) and a solution of acetaldehyde (62.7 mg, 1.42 mmol) in dichloromethane (2.5 mL) were added. The reaction mixture was stirred for 30 min at -95 °C and then saturated aqueous sodium hydrogencarbonate was added. The mixture was filtrated through a short pad of Celite and extracted with dichloromethane, 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 / 4) to afford a mixture of aldols (**4**)

and (**ent-4**) (85.9 mg, 78%) as a colorless oil: $[\alpha]_{\text{D}}^{25} = -41.6^\circ$ (c 1.60, CHCl_3) (96% ee); IR (neat): 3450, 1690 cm^{-1} ; ^1H NMR(CDCl_3): δ 4.24 (dddq, 1H, $J = 7.6, 3.6, 3.3, 6.3$ Hz, 3-H), 2.90 (q, 2H, $J = 7.4$ Hz, 1'-H), 2.74 (br d, 1H, $J = 3.3$ Hz, OH), 2.73 (dd, 1H, $J = 15.5, 3.6$ Hz, 2-H), 2.66 (dd, 1H, $J = 15.5, 7.6$ Hz, 2-H), 1.26 (t, 3H, $J = 7.4$ Hz, 2'-H), 1.22 (d, 3H, $J = 6.3$ Hz, 4-H); ^{13}C NMR(CDCl_3): δ 199.9 (1), 65.2 (3), 52.4 (2), 23.7 (4), 22.8 (1'), 14.9 (2'); HPLC (CHIRALCEL OD, *i*-PrOH / hexane = 1 / 100, flow rate = 1.0 mL / min): $t_{\text{R}} = 20.2$ min (98.0%), $t_{\text{R}} = 23.8$ min (2.0%).

S-Ethyl (S)-3-hydroxybutanoate (ent-4):¹⁷ Chiral diamine (**3'**) was prepared starting from D-proline by a literature method.¹⁵ To a suspension of tin(II) trifluoromethanesulfonate (278 mg, 0.666 mmol) in dichloromethane (2.5 mL) at rt were added a solution of chiral diamine (**3'**) (197 mg, 0.804 mmol) in dichloromethane (2.4 mL) and tributyltin fluoride (229 mg, 0.741 mmol). After the reaction mixture had been stirred for 10 min at -95°C , a solution of 1-ethylthio-1-(trimethylsiloxy)ethene (81.5 mg, 0.462 mmol) in dichloromethane (2 mL) and a solution of acetaldehyde (39.1 mg, 0.888 mmol) in dichloromethane (2 mL) were added. The reaction mixture was stirred for 30 min at -95°C and then saturated aqueous sodium hydrogencarbonate was added. The mixture was filtrated through a short pad of Celite and extracted with dichloromethane, 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 / 4) to afford a mixture of aldols (**4**) and (**ent-4**) (57.5 mg, 83%) as a colorless oil: $[\alpha]_{\text{D}}^{25} = +41.1^\circ$ (c 1.00, CHCl_3) (96% ee); HPLC (CHIRALCEL OD, *i*-PrOH / hexane = 1 / 100, flow rate = 1.0 mL / min): $t_{\text{R}} = 20.4$ min (1.9%), $t_{\text{R}} = 23.5$ min (98.1%).

S-Ethyl (R)-3-(tert-butyldimethylsiloxy)butanoate (5): To a solution of aldol (**4**) (36.9 mg, 0.248 mmol) in dichloromethane (2 mL) at 0°C were added a solution of 2,6-lutidine (101 mg, 0.941 mmol) in dichloromethane (0.8 mL) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (119 mg, 0.446 mmol) in dichloromethane (0.8 mL). The reaction mixture was stirred for 1 h at 0°C and then saturated aqueous sodium chloride was added. The mixture was 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 preparative thin layer chromatography (AcOEt / hexane = 1 / 6) to afford thiol ester (**5**) (62.2 mg, 96%) as a colorless oil: $[\alpha]_{\text{D}}^{24} = -46.2^\circ$ (c 1.67, CHCl_3) (96% ee); IR (neat): 1690 cm^{-1} ; ^1H NMR (CDCl_3): δ 4.28 (dddq, 1H, $J = 7.6, 5.1, 6.3$ Hz, 3-H), 2.84 (q, 2H, $J = 7.4$ Hz, 1'-H), 2.70

(dd, 1H, $J = 14.2, 7.6$ Hz, 2-H), 2.52 (dd, 1H, $J = 14.2, 5.1$ Hz, 2-H), 1.22 (t, 3H, $J = 7.4$ Hz, 2'-H), 1.16 (d, 3H, $J = 6.3$ Hz, 4-H), 0.84 (s, 9H, TBS), 0.03 (s, 3H, TBS), 0.01 (s, 3H, TBS); ^{13}C NMR(CDCl_3): δ 197.7 (1), 66.0 (3), 53.8 (2), 25.7 (TBS), 23.8 (4), 23.3 (1'), 18.0 (TBS), 14.6 (2'), -4.6 (TBS), -5.1 (TBS); Anal: calcd for $\text{C}_{12}\text{H}_{26}\text{O}_2\text{SSi}$: C, 54.91; H, 9.98, found: C, 54.80; H, 9.98; EI MS: calcd for $\text{C}_{11}\text{H}_{23}\text{O}_2\text{SSi}$ ($\text{M}^+ - \text{Me}$) 247.1, found 247.1; EI MS: calcd for $\text{C}_8\text{H}_{17}\text{O}_2\text{SSi}$ ($\text{M}^+ - t\text{-Bu}$) 205.1, found 204.9.

(*R*)-3-(*tert*-Butyldimethylsiloxy)butanal (6):^{5,18} To a solution of thiol ester (**5**) (57.3 mg, 0.218 mmol) in toluene (2 mL) at -78°C was added DIBAL in toluene (1.0 M, 0.22 mL, 0.220 mmol). After the reaction mixture had been stirred for 2 h at -78°C , methanol (0.5 mL) was added. The reaction mixture was allowed to warm to rt and then saturated aqueous potassium sodium tartrate (3 mL) was added. 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 / 10) to afford aldehyde (**6**) (37.2 mg, 84%) as a colorless oil: $[\alpha]_{\text{D}}^{24} = -18.2^\circ$ (c 1.00, CHCl_3) (96% ee); IR (neat): 1720 cm^{-1} ; ^1H NMR (CDCl_3): δ 9.79 (t, 1H, $J = 2.6$ Hz, CHO), 4.34 (ddq, 1H, $J = 6.8, 5.1, 5.9$ Hz, 3-H), 2.54 (ddd, 1H, $J = 15.8, 6.8, 2.6$ Hz, 2-H), 2.45 (ddd, 1H, $J = 15.8, 5.1, 2.6$ Hz, 2-H), 1.23 (d, 3H, $J = 5.9$ Hz, 4-H), 0.86 (s, 9H, TBS), 0.07 (s, 3H, TBS), 0.06 (s, 3H, TBS); ^{13}C NMR (CDCl_3): δ 202.0 (1), 64.5 (3), 52.9 (2), 25.6 (TBS), 24.1 (4), 17.8 (TBS), -4.5 (TBS), -5.0 (TBS).

Ethyl (*R*)-5-(*tert*-butyldimethylsiloxy)-*trans*-2-hexenoate (7):^{18,19} To a suspension of sodium hydride (55%, 2.21 g, 50.6 mmol) in THF (80 mL) at 0°C was added a solution of triethyl phosphonoacetate (11.3 g, 50.4 mmol) in THF (50 mL). After the reaction mixture had been stirred for 30 min at rt, a solution of aldehyde (**6**) (1.12 g, 5.53 mmol) in THF (20 mL) was added at 0°C . The reaction mixture was stirred for 1 h at 0°C and then water was added. The mixture was extracted with ether, and the organic layer was washed with water and brine. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography (AcOEt / hexane = 1 / 30) to afford ester (**7**) (10.4 g, 83%) as a colorless oil: $[\alpha]_{\text{D}}^{24} = -10.1^\circ$ (c 1.65, CHCl_3) (96% ee); IR (neat): 1720 cm^{-1} ; ^1H NMR (CDCl_3): δ 6.94 (dt, 1H, $J = 15.5, 7.6$ Hz, 3-H), 5.82 (ddd, 1H, $J = 15.5, 1.6, 1.3$ Hz, 2-H), 4.18 (q, 2H, $J = 7.3$ Hz, 1'-H), 3.91 (ddq, $J = 6.3, 5.9, 6.3$ Hz, 1H, 5-H), 2.34 (ddd, $J = 7.6, 6.3, 1.3$ Hz, 1H, 4-H), 2.26 (ddd, $J = 7.6,$

5.9, 1.6 Hz, 1H, 4-H), 1.27 (t, 3H, $J = 7.3$ Hz, 2'-H), 1.15 (d, 3H, $J = 6.3$ Hz, 6-H), 0.87 (s, 9H, TBS), 0.04 (s, 3H, TBS), 0.03 (s, 3H, TBS); ^{13}C NMR (CDCl_3): δ 166.4 (1), 146.0 (3), 123.2 (2), 67.6 (5), 60.1 (1'), 42.4 (4), 25.8 (TBS), 23.8 (6), 18.1 (TBS), 14.2 (2'), -4.6 (TBS), -4.9 (TBS); EI MS: calcd for $\text{C}_{10}\text{H}_{19}\text{O}_3\text{Si}$ ($\text{M}^+ - \text{Me}$) 257.2, found 257.2; EI MS: calcd for $\text{C}_{10}\text{H}_{19}\text{O}_3\text{Si}$ ($\text{M}^+ - t\text{-Bu}$) 215.1, found 215.1.

Ethyl (*R*)-5-(*tert*-butyldimethylsiloxy)hexanoate (8):¹⁹ To a solution of ester (7) (23.2 g, 85.3 mmol) in ethanol (250 mL) was added palladium on activated carbon (10%, 1.50 g). The reaction mixture was stirred for 10 h at rt under hydrogen atmosphere. The mixture was filtered through a short pad of Celite and concentrated by evaporation of the solvent to afford ester (8) (22.1 g, 95%) as a colorless oil: $[\alpha]_{\text{D}}^{23} = -23.3^\circ$ (c 1.00, benzene) (96% ee); IR (neat): 1740 cm^{-1} ; ^1H NMR (CDCl_3): δ 4.12 (q, 2H, $J = 7.3$ Hz, 1'-H), 3.79 (tq, $J = 5.9, 6.3$ Hz, 1H, 5-H), 2.29 (t, 2H, $J = 7.4$ Hz, 2-H), 1.91-1.34 (m, 4H, 3-H, 4-H), 1.25 (t, 2H, $J = 7.3$ Hz, 2'-H), 1.12 (d, 3H, $J = 6.3$ Hz, 6-H), 0.88 (s, 9H, TBS), 0.04 (s, 6H, TBS); ^{13}C NMR(CDCl_3): δ 173.7 (1), 68.2 (5), 60.1 (1'), 39.0 (4), 34.3 (2), 25.9 (TBS), 23.7 (6), 21.3 (3), 18.1 (TBS), 14.2 (2'), -4.4 (TBS), -4.8 (TBS); EI MS: calcd for $\text{C}_{10}\text{H}_{21}\text{O}_3\text{Si}$ ($\text{M}^+ - \text{Me}$) 259.2, found 259.4; EI MS: calcd for $\text{C}_{10}\text{H}_{21}\text{O}_3\text{Si}$ ($\text{M}^+ - t\text{-Bu}$) 217.1, found 217.1.

(*R*)-5-(*tert*-Butyldimethylsiloxy)hexanal (9):²⁰

To a solution of the above crude ester (8) (7.03 g, 25.6 mmol) in toluene (90 mL) at -78°C was added DIBAL in toluene (1.0 M, 28.2 mL, 28.2 mmol). After the reaction mixture had been stirred for 2 h at -78°C , methanol (3.8 mL) was added. The reaction mixture was allowed to warm to rt and then saturated aqueous potassium sodium tartrate (90 mL) was added. 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 column chromatography (AcOEt / hexane = from 1 / 30 to 1 / 15) to afford aldehyde (9) (5.31 g, 90%) as a colorless oil. The aldehyde (9) was stored in a refrigerator after distillation under reduced pressure. bp $73^\circ\text{C} / 0.3\text{ mmHg}$; $[\alpha]_{\text{D}}^{23} = -27.1^\circ$ (c 1.00, benzene) (96% ee); IR (neat): 1730 cm^{-1} ; ^1H NMR (CDCl_3): δ 9.76 (t, 1H, $J = 1.7$ Hz, CHO), 3.81 (tq, $J = 5.9, 6.3$ Hz, 1H, 5-H), 2.43 (dt, 2H, $J = 1.7, 7.3$ Hz, 2-H), 1.82-1.35 (m, 4H, 3-H, 4-H), 1.13 (d, 3H, $J = 6.3$ Hz, 6-H), 0.88 (s, 9H, TBS), 0.05 (s, 3H, TBS), 0.04 (s, 3H, TBS); ^{13}C NMR(CDCl_3): δ 202.7 (1), 68.1 (5), 43.9 (2), 38.9 (4), 25.9 (TBS), 23.7 (6), 18.3 (3), 18.1 (TBS), -4.4 (TBS), -4.8 (TBS).

S-Ethyl (3*S*,7*R*)-7-(*tert*-butyldimethylsiloxy)-3-hydroxyoctanoate (10): To a suspension of tin(II) trifluoromethanesulfonate (164 mg, 0.393 mmol) in dichloromethane (0.5 mL) at rt were added a solution of chiral diamine (**3'**) (113 mg, 0.472 mmol) in dichloromethane (0.5 mL) and tributyltin fluoride (134 mg, 0.433 mmol). After the reaction mixture had been stirred for 10 min at -78 °C, a solution of 1-ethylthio-1-(trimethylsiloxy)ethene (69.3 mg, 0.393 mmol) in dichloromethane (0.5 mL) and a solution of aldehyde (**9**) (61.0 mg, 0.264 mmol) in dichloromethane (1 mL) were added. The reaction mixture was stirred for 3 h at -78 °C and then saturated aqueous sodium hydrogencarbonate was added. The mixture was filtrated through a short pad of Celite and extracted with dichloromethane, and the organic layer was washed with brine, and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the residue was dissolved in a mixture of hydrochloric acid (1.0 M, 0.5 mL) and THF (9.5 mL). The mixture was stirred for 30 min and then hexane (5 mL) and aqueous sodium hydrogencarbonate (10 mL) were added at 0 °C. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine, 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 / 6) to afford a mixture of aldols (**10**) and (**10'**) (**10** / **10'** = 97 / 3, 78.1 mg, 89%) as a colorless oil. **Aldol (10):** $[\alpha]_{\text{D}}^{24} = -3.0^{\circ}$ (c 1.00, benzene) (**10** / **10'** = 98 / 2); IR (neat): 1680 cm^{-1} ; ^1H NMR (CDCl_3): δ 4.09-3.96 (m, 1H, 3-H), 3.77 (tq, $J = 5.6, 5.9$ Hz, 1H, 7-H), 2.89 (q, 2H, $J = 7.4$ Hz, 1'-H), 2.75 (dd, 1H, $J = 15.7, 4.0$ Hz, 2-H), 2.73 (br s, 1H, OH), 2.63 (dd, 1H, $J = 15.7, 8.1$ Hz, 2-H), 1.55-1.29 (m, 6H, 4-H, 5-H, 6-H), 1.25 (t, 3H, $J = 7.4$ Hz, 2'-H), 1.10 (d, 3H, $J = 5.9$ Hz, 8-H), 0.87 (s, 9H, TBS), 0.03 (s, 6H, TBS); ^{13}C NMR(CDCl_3): δ 199.5 (1), 68.6 (3), 68.4 (7), 50.6 (2), 39.4 (6), 36.6 (4), 25.9 (TBS), 23.7 (8), 23.3 (1'), 21.6 (5), 18.1 (TBS), 14.6 (2'), -4.4 (TBS), -4.7 (TBS); HPLC (CHIRALCEL OD, *i*-PrOH / hexane = 1 / 200, flow rate = 0.8 mL / min): $t_{\text{R}} = 13.1$ min (2.7%), $t_{\text{R}} = 14.9$ min (97.3%); HR-MS: calcd for $\text{C}_{16}\text{H}_{35}\text{O}_3\text{SSi}$ ($\text{M} + \text{H}^+$) 335.2077, found 335.1988.

S-Ethyl (3*R*,7*R*)-7-(*tert*-butyldimethylsiloxy)-3-hydroxyoctanoate (10'): To a suspension of tin(II) trifluoromethanesulfonate (165 mg, 0.397 mmol) in dichloromethane (0.5 mL) at rt were added a solution of chiral diamine (**3**) (114 mg, 0.476 mmol) in dichloromethane (0.5 mL) and tributyltin fluoride (135 mg, 0.436 mmol). After the reaction mixture had been stirred for 10 min at -78 °C, a solution of 1-ethylthio-1-(trimethylsiloxy)ethene (69.9 mg, 0.397 mmol) in dichloromethane (0.5 mL) and a solution of aldehyde (**9**) (61.7 mg, 0.268 mmol) in dichloromethane (1 mL) were added. The reaction mixture was stirred for 3 h at

-78 °C and then saturated aqueous sodium hydrogencarbonate was added. The mixture was filtrated through a short pad of Celite and extracted with dichloromethane, 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 / 6) to afford a mixture of aldols (**10**) and (**10'**) (**10** / **10'** = 3 / 97, 51.3 mg, 62%) as a colorless oil. **Aldol (10')**: $[\alpha]_{\text{D}}^{25} = -37.5^\circ$ (c 2.01, benzene) (**10** / **10'** = 6 / 94); IR (neat): 3510, 1680 cm^{-1} ; ^1H NMR (CDCl_3): δ 4.10-3.97 (m, 1H, 3-H), 3.77 (tq, 1H, $J = 5.8, 6.3$ Hz, 7-H), 2.89 (q, 2H, $J = 7.4$ Hz, 1'-H), 2.75 (dd, 1H, $J = 15.5, 3.6$ Hz, 2-H), 2.72 (br s, 1H, OH), 2.63 (dd, 1H, $J = 15.5, 8.3$ Hz, 2-H), 1.57-1.30 (m, 6H, 4-H, 5-H, 6-H), 1.26 (t, 3H, $J = 7.4$ Hz, 2'-H), 1.11 (d, 3H, $J = 6.3$ Hz, 8-H), 0.87 (s, 9H, TBS), 0.03 (s, 6H, TBS); ^{13}C NMR(CDCl_3): δ 199.7 (1), 68.6 (3), 68.4 (7), 50.6 (2), 39.4 (6), 36.5 (4), 25.9 (TBS), 23.7 (8), 23.3 (1'), 21.7 (5), 18.1 (TBS), 14.6 (2'), -4.4 (TBS), -4.7 (TBS); HPLC (CHIRALCEL OD, *i*-PrOH / hexane = 1 / 200, flow rate = 0.8 mL / min): $t_{\text{R}} = 13.7$ min (96.7%), $t_{\text{R}} = 16.7$ min (3.3%); HR MS: calcd for $\text{C}_{16}\text{H}_{34}\text{O}_3\text{NaSSi}$ ($\text{M} + \text{Na}^+$) 357.1896, found 357.1930.

Ethyl (3*S*,7*R*)-7-(*tert*-butyldimethylsiloxy)-3-hydroxyoctanoate (11): To a solution of aldols (**10**) and (**10'**) (**10** / **10'** = 94 / 6, 1.01 g, 3.02 mmol) in methanol (4 mL) were added a solution of *N,N*-diisopropylethylamine (1.52 g, 11.8 mmol) in methanol (2 mL) and silver trifluoroacetate (1.20 g, 5.44 mmol). The reaction mixture was stirred for 10 h at rt and then water was added at 0 °C. The mixture was filtrated through a short pad of Celite and 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 / 10) to afford a mixture of esters (**11**) and (**11'**) (**11** / **11'** = 94 / 6, 894 mg, 93%) as a colorless oil. **Ester (11)**: $[\alpha]_{\text{D}}^{24} = -10.0^\circ$ (c 1.00, benzene) (**11** / **11'** = 98 / 2); IR (neat): 3440, 1730 cm^{-1} ; ^1H NMR (CDCl_3): δ 4.17 (q, 2H, $J = 7.1$ Hz, 1'-H), 4.02-3.89 (m, 1H, 3-H), 3.78 (tq, 1H, $J = 5.9, 6.3$ Hz, 7-H), 2.95 (br d, 1H, $J = 4.0$ Hz, OH), 2.50 (dd, 1H, $J = 16.5, 3.3$ Hz, 2-H), 2.38 (dd, 1H, $J = 16.5, 8.6$ Hz, 2-H), 1.56-1.28 (m, 6H, 4-H, 5-H, 6-H), 1.27 (t, 3H, $J = 7.1$ Hz, 2'-H), 1.11 (d, 3H, $J = 6.3$ Hz, 8-H), 0.88 (s, 9H, TBS), 0.04 (s, 6H, TBS); ^{13}C NMR (CDCl_3): δ 173.0 (1), 68.4 (7), 68.0 (3), 60.6 (1'), 41.2 (2), 40.0 (6), 36.6 (4), 25.9 (TBS), 23.7 (8), 21.7 (5), 18.1 (TBS), 14.1 (2'), -4.4 (TBS), -4.7 (TBS); HR MS: calcd for $\text{C}_{16}\text{H}_{34}\text{O}_4\text{NaSi}$ ($\text{M} + \text{Na}^+$) 341.2124, found 341.2204.

Ethyl (3*S*,7*R*)-3-benzyloxy-7-(*tert*-butyldimethylsiloxy)octanoate (12): To a solution of esters (11) and (11') (11 / 11' = 94 / 6, 888 mg, 2.79 mmol) and benzyl trichloroacetimidate (1.76 g, 6.97 mmol) in dichloromethane (7 mL) was added a solution of trifluoromethanesulfonic acid (62.8 mg, 0.419 mmol) in dichloromethane (0.33 mL). After the reaction mixture had been stirred for 30 min at rt, sodium hydrogencarbonate and water were added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over sodium sulfate. The mixture was filtrated and concentrated by evaporation of the solvent and then hexane was added to the residue. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography (AcOEt / hexane = 1 / 3) to afford a mixture of esters (12) and (12') (12 / 12' = 94 / 6, 970 mg, 85%) and a mixture of esters (13) and (13') (13 / 13' = 94 / 6, 75.1 mg, 9%) as colorless oils. **Ester (12):** $[\alpha]_{\text{D}}^{26} = -12.9^\circ$ (c 1.00, benzene) (12 / 12' = 98 / 2); IR (neat): 1730 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.39-7.20 (m, 5H, Ph), 4.57 (d, 1H, $J = 11.5$ Hz, Bn-H), 4.52 (d, 1H, $J = 11.5$ Hz, Bn-H), 4.10 (q, 2H, $J = 7.3$ Hz, 1'-H), 3.95-3.82 (m, 1H, 3-H), 3.78 (tq, 1H, $J = 5.9, 6.3$ Hz, 7-H), 2.61 (dd, 1H, $J = 15.2, 7.3$ Hz, 2-H), 2.46 (dd, 1H, $J = 15.2, 5.6$ Hz, 2-H), 1.70-1.31 (m, 6H, 4-H, 5-H, 6-H), 1.25 (t, 3H, $J = 7.3$ Hz, 2'-H), 1.11 (d, 3H, $J = 6.1$ Hz, 8-H), 0.88 (s, 9H, TBS), 0.04 (s, 6H, TBS); ^{13}C NMR(CDCl_3): δ 172.2 (1), 138.9 (Ph), 128.7 (Ph), 128.1 (Ph), 127.9 (Ph), 76.5 (3), 72.0 (Bn), 68.9 (7), 60.8 (1'), 40.4 (2), 40.1 (6), 35.0 (4), 26.3 (TBS), 24.2 (8), 21.9 (5), 18.5 (TBS), 14.6 (2'), -4.0 (TBS), -4.3 (TBS); Anal: calcd for $\text{C}_{23}\text{H}_{40}\text{O}_4\text{Si}$: C, 67.60; H, 9.87, found: C, 67.51; H, 9.91; HR MS: calcd for $\text{C}_{23}\text{H}_{41}\text{O}_4\text{Si}$ ($\text{M} + \text{H}^+$) 409.2775, found 409.2769.

Ethyl (3*S*,7*R*)-3-benzyloxy-7-hydroxyoctanoate (13): To the mixture of esters (12) and (12') (12 / 12' = 94 / 6, 971 mg, 2.37 mmol) at 0 °C was added a mixture of acetic acid (9 mL), water (3 mL) and THF (3 mL). After the reaction mixture had been stirred for 10 h at rt, it was neutralized with aqueous potassium hydroxide (16 M) 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 / 1) to afford a mixture of esters (13) and (13') (13 / 13' = 94 / 6, 662 mg, 95%) as a colorless oil. **Ester (13):** $[\alpha]_{\text{D}}^{25} = -6.3^\circ$ (c 1.00, CHCl_3) (13 / 13' = 98 / 2); IR (neat): 3380, 1730 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.42-7.06 (m, 5H, Ph), 4.57 (d, 1H, $J = 11.6$ Hz, Bn-H), 4.51 (d, 1H, $J = 11.6$ Hz, Bn-H), 4.14 (q, 2H, $J = 7.3$ Hz, 1'-H), 3.94-3.82 (m, 1H, 3-H), 3.82-3.70 (m, 1H, 7-H), 2.63 (dd, 1H, $J = 15.0, 7.1$ Hz, 2-H), 2.47 (dd, 1H,

$J = 15.0, 5.8$ Hz, 2-H), 1.83-1.31 (m, 6H, 4-H, 5-H, 6-H), 1.25 (t, 3H, $J = 7.3$ Hz, 2'-H), 1.17 (d, 3H, $J = 6.3$ Hz, 8-H); ^{13}C NMR(CDCl_3): δ 171.7 (1), 138.3 (Ph), 128.8 (Ph), 128.2 (Ph), 127.7 (Ph), 75.9 (3), 71.5 (Bn), 67.6 (7), 60.4 (1'), 39.8 (2), 39.0 (6), 34.2 (4), 23.4 (8), 21.3 (5), 14.1 (2'); HR MS: calcd for $\text{C}_{17}\text{H}_{27}\text{O}_4$ ($\text{M} + \text{H}^+$) 295.1909, found 295.2006.

(3*S*,7*R*)-3-Benzoyloxy-7-hydroxyoctanoic acid (14): To a solution of esters (**13**) and (**13'**) (**13** / **13'** = 94 / 6, 737 mg, 2.50 mmol) in methanol (6.2 mL) was added aqueous potassium hydroxide (17 M, 0.623 mL, 10.6 mmol). The reaction mixture was stirred for 3 h at rt and then neutralized with hydrochloric acid (4 M) 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 (AcOH / AcOEt / hexane = 9 / 100 / 200) to afford a mixture of carboxylic acid (**14**) and (**14'**) (**14** / **14'** = 94 / 6, 447 mg, 67%) as a colorless oil. **Carboxylic acid (14):** $[\alpha]_{\text{D}}^{25} = -7.3^\circ$ (c 1.00, CHCl_3) (**14** / **14'** = 98 / 2); IR (neat): 3400, 1710 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.40-7.20 (m, 5H, Ph), 5.68 (br s, 2H, OH, COOH), 4.58 (d, 1H, $J = 11.4$ Hz, Bn-H), 4.51 (d, 1H, $J = 11.4$ Hz, Bn-H), 3.94-3.82 (m, 1H, 3-H), 3.82-3.69 (m, 1H, 7-H), 2.65 (dd, 1H, $J = 15.5, 6.6$ Hz, 2-H), 2.51 (dd, 1H, $J = 15.5, 5.8$ Hz, 2-H), 1.74-1.29 (m, 6H, 4-H, 5-H, 6-H), 1.16 (d, 3H, $J = 6.3$ Hz, 8-H); ^{13}C NMR(CDCl_3): δ 176.4 (1), 138.1 (Ph), 128.4 (Ph), 127.9 (Ph), 127.7 (Ph), 75.7 (3), 71.5 (Bn), 67.9 (7), 39.5 (2), 38.9 (6), 34.1 (4), 23.4 (8), 21.2 (5); HR MS: calcd for $\text{C}_{15}\text{H}_{23}\text{O}_4$ ($\text{M} + \text{H}^+$) 267.1597, found 267.1656; HR MS: calcd for $\text{C}_{15}\text{H}_{22}\text{O}_4\text{Na}$ ($\text{M} + \text{Na}^+$) 289.1416, found 289.1366.

(-)-Benzoyloxycephalosporolide D (15): To a solution of hafnium tetrakis(trifluoromethanesulfonate) (31.2 mg, 40.3 μmol) and 4-trifluoromethylbenzoic anhydride (146 mg, 0.403 mmol) in acetonitrile (116 mL) at reflux temperature was added a solution of carboxylic acids (**14**) and (**14'**) (**14** / **14'** = 94 / 6, 53.7 mg, 0.202 mmol) in THF (5 mL) over 8 h period by use of a mechanically driven syringe. After the reaction mixture had been stirred for 2 h at reflux temperature, saturated aqueous sodium hydrogencarbonate (2.1 mL) was added at rt. The mixture was concentrated by evaporation of the solvent and then it was extracted with ether, 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 / 4) to afford a mixture of lactones (**15**) and (**15'**) (**15** / **15'** = 94 / 6, 23.5 mg, 47%) and recovered starting materials (**14** / **14'** = 94 / 6, 20.8 mg, 39%) as a colorless oils.

Lactone (15): $[\alpha]_D^{26} = -78.2^\circ$ (c 1.00, CHCl_3) (**15** / **15'** = 98 / 2); IR (neat): 1720 cm^{-1} ; ^1H NMR (CDCl_3): δ 7.39-7.14 (m, 5H, Ph), 4.69 (ddq, 1H, $J = 10.5, 5.3, 6.3\text{ Hz}$, 7-H), 4.61 (d, 1H, $J = 11.9\text{ Hz}$, Bn-H), 4.44 (d, 1H, $J = 11.9\text{ Hz}$, Bn-H), 3.77-3.62 (m, 1H, 3-H), 2.71 (dd, 1H, $J = 11.9, 4.3\text{ Hz}$, 2-H), 2.67 (dd, 1H, $J = 11.9, 6.6\text{ Hz}$, 2-H), 1.96-1.46 (m, 5H, 4-H, 5-H, 6-H), 1.33-1.02 (m, 1H, 5-H), 1.26 (d, 3H, $J = 6.3\text{ Hz}$, 8-H); ^{13}C NMR(CDCl_3): δ 172.3 (1), 138.1 (Ph), 128.3 (Ph), 127.6 (Ph), 127.5 (Ph), 77.3 (3), 75.3 (7), 70.1 (Bn), 38.3 (6), 37.7 (2), 32.9 (4), 21.3 (8), 18.9 (5); Anal: calcd for $\text{C}_{15}\text{H}_{20}\text{O}_3$: C, 72.55; H, 8.12, found: C, 72.15; H, 8.03; HR MS: calcd for $\text{C}_{15}\text{H}_{21}\text{O}_3\text{Na}$ ($\text{M} + \text{Na}^+$) 249.1491, found 249.1539.

Lactone (15'): ^1H NMR (CDCl_3): δ 7.45-7.19 (m, 5H, Ph), 4.83-4.63 (m, 1H, 7-H), 4.69 (d, 1H, $J = 11.9\text{ Hz}$, Bn-H), 4.51 (d, 1H, $J = 11.9\text{ Hz}$, Bn-H), 3.84-3.69 (m, 1H, 3-H), 2.88 (dd, 1H, $J = 11.9, 3.0\text{ Hz}$, 2-H), 2.73 (dd, 1H, $J = 11.9, 3.0\text{ Hz}$, 2-H), 2.05-1.54 (m, 5H, 4-H, 5-H, 6-H), 1.47-1.06 (m, 1H, 5-H), 1.33 (d, 3H, $J = 5.9\text{ Hz}$, 8-H); ^{13}C NMR(CDCl_3): δ 172.3 (1), 138.1 (Ph), 128.4 (Ph), 127.6 (Ph), 127.5 (Ph), 76.7 (3), 75.3 (7), 70.7 (Bn), 38.0 (6), 37.3 (2), 31.8 (4), 21.5 (8), 18.7 (5).

(4*S*,8*R*,12*S*,16*R*)-4,12-Dibenzyloxy-8,16-dimethyl-1,9-dioxacyclohexadecane-2,10-tetron (16): IR (neat): 1730 cm^{-1} ; ^1H NMR (C_6D_6): δ 7.30-7.15 (m, 10H, Ph), 4.85 (m, 2H, 8-H, 16-H), 4.48 (d, 2H, $J = 11.9\text{ Hz}$, Bn-H, Bn-H), 4.42 (d, 2H, $J = 11.9\text{ Hz}$, Bn-H, Bn-H), 3.88 (m, 2H, 4-H, 12-H), 2.69 (dd, 2H, $J = 15.8, 3.3\text{ Hz}$, 3-H, 11-H), 2.51 (dd, 2H, $J = 15.8, 9.9\text{ Hz}$, 3-H, 11-H), 1.70-1.20 (m, 12H, 5-H, 6-H, 7-H, 13-H, 14-H, 15-H), 1.12 (d, 6H, $J = 6.6\text{ Hz}$, Me, Me); ^{13}C NMR(C_6D_6): δ 170.9 (2, 10), 139.4 (Ph, Ph), 128.4 (Ph, Ph), 128.0 (Ph, Ph), 127.6 (Ph, Ph), 75.6 (4, 12), 70.7 (Bn, Bn), 70.2 (8, 16), 38.7 (5, 13), 36.2 (3, 11), 33.9 (7, 15), 20.4 (6, 14), 19.6 (9, 17); FAB MS: calcd for $\text{C}_{30}\text{H}_{41}\text{O}_6$ ($\text{M} + \text{H}^+$) 497, found 497; FAB MS: calcd for $\text{C}_{30}\text{H}_{40}\text{O}_6\text{Na}$ ($\text{M} + \text{Na}^+$) 519, found 519.

(-)-Cephalosporolide D (1):¹ To a solution of lactones (**15**) and (**15'**) (**15** / **15'** = 94 / 6, 216 mg, 0.869 mmol) in ethanol (12 mL) was added palladium on activated carbon (10%, 367 mg). After the reaction mixture had been stirred for 10 h at rt under hydrogen atmosphere, palladium on activated carbon (10%, 361 mg) was added under the argon atmosphere. The reaction mixture was stirred for 10 h at rt under hydrogen atmosphere and then palladium on activated carbon (10%, 366 mg) was added under the argon atmosphere. The reaction mixture was stirred for 30 h at rt under hydrogen atmosphere. After the mixture was filtrated through a short pad of Celite and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography (AcOEt / hexane = 1 / 1) to afford a mixture of lactones (**1**) and (*ent*-**1'**) (**1** / *ent*-**1'** =

94 / 6, 90.6 mg, 66%) and recovered starting materials (**15** / **15'** = 94 / 6, 20.8 mg, 10%) as a white solid. First recrystallization of the mixture of lactones (**1**) and (**ent-1'**) (**1** / **ent-1'** = 94 / 6) from hexane gave optically pure lactone (**1**) as colorless needles: mp 131 °C; $[\alpha]_D^{28} = -46.8^\circ$ (c 2.40, CHCl₃); IR (KBr): 3430, 1690 cm⁻¹; ¹H NMR (CDCl₃): δ 4.69 (ddq, *J* = 10.2, 3.1, 5.9 Hz, 1H, 7-H), 4.16-3.97 (m, 1H, 3-H), 2.93 (dd, 1H, *J* = 12.4, 3.8 Hz, 2-H), 2.60 (dd, 1H, *J* = 12.4, 5.8 Hz, 2-H), 1.92-1.50 (m, 5H, 4-H, 5-H, 6-H), 1.38-1.02 (m, 1H, 5-H), 1.35 (d, 3H, *J* = 5.9 Hz, 8-H); ¹³C NMR(CDCl₃): δ 173.0 (1), 76.3 (7), 69.5 (3), 39.4 (2), 38.3 (6), 34.7 (4), 21.7 (8), 18.9 (5); HR MS: calcd for C₈H₁₄O₃Na (M + Na⁺) 181.0840, found 181.0817. **Epicephalosporolide D (ent-1')**: ¹H NMR (CDCl₃): δ 4.82-4.66 (m, 1H, 7-H), 4.21-4.04 (m, 1H, 3-H), 2.79 (ddd, 1H, *J* = 12.2, 5.9, 0.7 Hz, 2-H), 2.74 (dd, 1H, *J* = 12.2, 8.9 Hz, 2-H), 2.05-1.55 (m, 5H, 4-H, 5-H, 6-H), 1.44-1.18 (m, 1H, 5-H), 1.36 (d, 3H, *J* = 5.9 Hz, 8-H); ¹³C NMR(CDCl₃): δ 172.3 (1), 75.1 (7), 70.6 (3), 40.6 (2), 38.1 (6), 35.0 (4), 21.4 (8), 18.4 (5).

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