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Stereoselective synthesis (+)-cephalosporolide D

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ABSTRACT

A simple and efficient stereoselective synthesis of macrolactone, (+)-cephalosporolide D has been accomplished in 13 steps from inexpensive and commercially available starting materials in an overall yield of 17%, respectively. This convergent synthesis utilizes Maruoka asymmetric allylation reaction, Grubb's cross metathesis for the formation of a fully functionalized acid, and Yamaguchi lactonization as key steps.

Medium-sized ring systems are found in many biologically active molecules and natural products.[1] Medium ring compounds, and particularly lactones, have become an important class of compounds in organic chemistry, and now their chemistry cannot be considered as marginal. Cephalosporolides are a group of naturally occurring macrolides isolated from fermentation fungus, *cephalosporium aphidicola* ACC 3490.[2] The gross structures were established by extensive, IR, mass spectroscopy and NMR (1D and 2D) studies. Structurally, cephalosporolide D contains two chiral centers (C-4 and C-8) and unusual saturated eight-membered lactone ring that represents a prominent member of the saturated eight-membered lactone ring family of natural products that includes octalactin A and octalactin B (Fig. 1).[3] Because of their fascinating structural features and interesting biological properties, cephalosporolides have solicited considerable interest among organic chemists.[4] As a consequence of the central role played by this lactone ring system, numerous methods have been devised for the asymmetric synthesis of cephalosporolides.

Interests of these compounds have largely focused on the construction of eight-membered lactone ring system as well as the structural moiety possessing the asymmetric centers bearing a hydroxyl group and methyl group. Shiina et al. reported the synthesis of cephalosporolides which involved the eight-membered lactone moiety by a novel mixed anhydride method using (4-trifluoromethyl) benzoic anhydride (TFBA).[5] Also, Shiina has reviewed quite recently on the synthesis of eight-membered lactones.[6]

Our research program directed toward the expedient synthesis of polysubstituted piperidines from cheap and readily available starting materials[7a,d] prompted us to develop a general approach for the stereocontrolled synthesis of medium-sized lactone ring compounds. The realization of this goal and an application to the efficient synthesis of (+)-cephalosporolide D (**1**) is presented herein.

During the course of our synthetic studies on developing simple routes for the asymmetric synthesis of bioactive natural products,[7b,c] we found that Marouka asymmetric allylation of aldehyde derivatives using (*S*)-BINOL and (*R*)-BINOL proceeded smoothly to provide homoallylic alcohols with the desired enantioselectivity.[7c] Thus, our retrosynthetic strategy (Scheme 1) relies on the Maruoka allylation approach starting from the 1,3-propanediol and well-known Grubb's cross metathesis.

As outlined retrosynthetically in Scheme 1, cephalosporolide D (**1**) could be obtained by Yamaguchi lactonization[8] of acid **4**, which could be provided by the oxidation of **5**. In the forward direction, key fragment **5** containing two stereogenic centers was envisaged to be obtained by Grubb's cross metathesis reaction of two fragments **6** and **7**. Fragment **7**, containing one stereogenic center, could be derived from aldehyde **8** via Maruoka allylation, which is conceived to be obtained through four-step sequence starting from the inexpensive 1,3-propanediol (**9**). The highlight of present total synthesis is the utilization of Maruoka asymmetric allylation which directs the stereochemistry at C-7. More importantly, we

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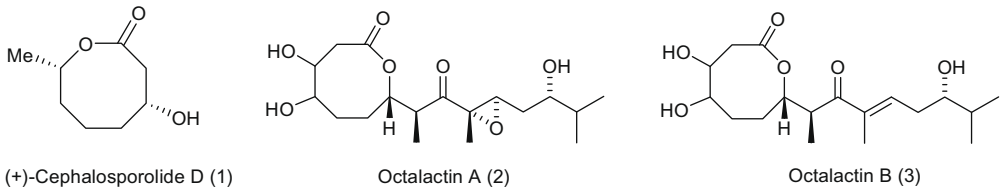
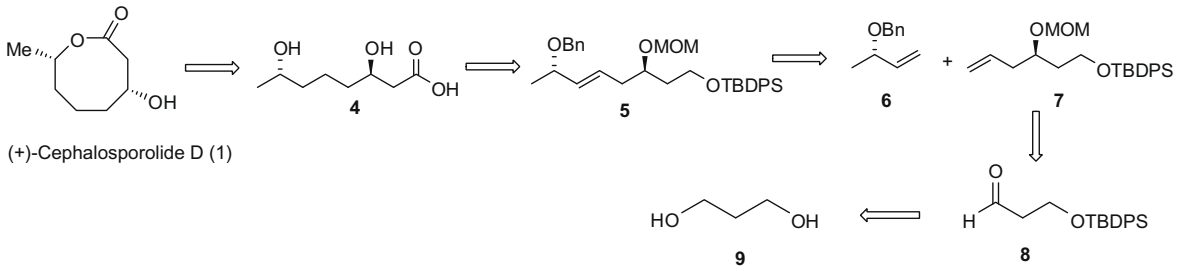
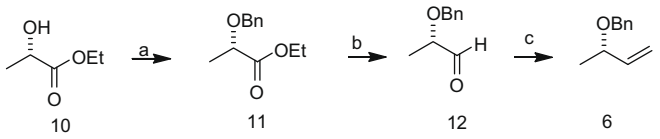


Figure 1. Structures of (+)-cephalosporolide D (**1**) and similar 8-membered lactones, octalactin A (**2**) and octalactin B (**3**).



Scheme 1. Retrosynthetic analysis of **1**.



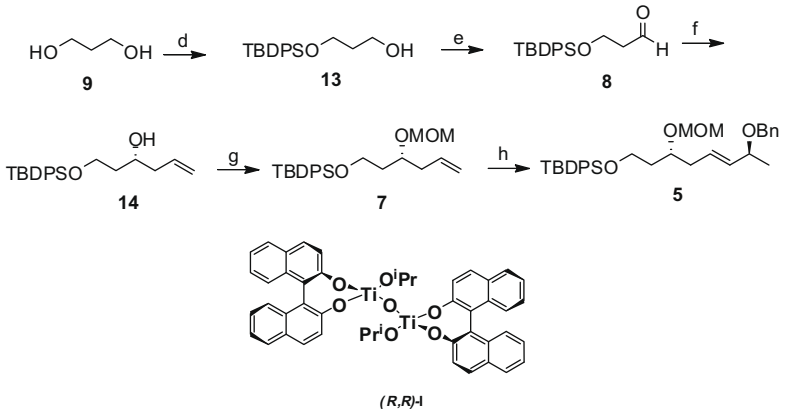
Scheme 2. Reagents and conditions: (a) BnBr, Ag_2O, Et_2O, reflux, 12 h, 90%; (b) DIBAL-H, CH_2Cl_2, −78 °C, 15 min, 88%; (c) CH_3IPPh_3, *t*-BuOK, toluene, 0 °C to rt, 1 h, 90%.

have successfully implemented a strategy that minimizes protecting group manipulation in a unique fashion, a common and unavoidable practice in cephalosporolide D synthesis.

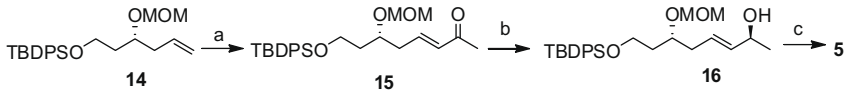
The synthesis of cephalosporolide D commenced from commercially available (*S*)-ethyl lactate (**10)** as chiral synthon. Thus, protection of the hydroxyl group with BnBr in the presence of Ag_2O in ether gave as its benzyl ether **11** in 90% yield,[9] which on reduction with DIBAL-H at −78 °C in dichloromethane leading to the corresponding aldehyde **12** in 88% yield.[9] Wittig olefination of **12** with *t*-BuOK in toluene proceeded smoothly to yield **6** in excellent yield (90%) (Scheme 2).

The journey for the synthesis of segment **7** began with the known 1,3-propanediol (**9**), which was selectively protected as TBDPS ether **13** using TBDPSCl, DIPEA in dry CH_2Cl_2 (Scheme 2).[10] IBX[11] oxidation of **13** yielded aldehyde **8**, which was subjected to an enantioselective Maruoka allylation[12] using titanium complex (*R,R*)-**I** and allyltri-*n*-butyltin to furnish the homoallylic alcohol **14** in 86% yield with excellent enantioselectivity of 98% ee (determined by chiral HPLC).[13] The resultant homoallylalcohol was orthogonally protected as its MOM ether **7** with MOMCl in the presence of DIPEA in CH_2Cl_2 at 0 °C to room temperature (90% yield).[14] The conjunction of precursors **6** and **7** was then investigated via olefin cross metathesis reaction. Treatment of the precursors **6** and **7** with second generation Grubb's catalyst (5 mol % Grubbs II) in dichloromethane under reflux conditions gratifyingly yielded **5** in 80% yield[15] (see Scheme 3).

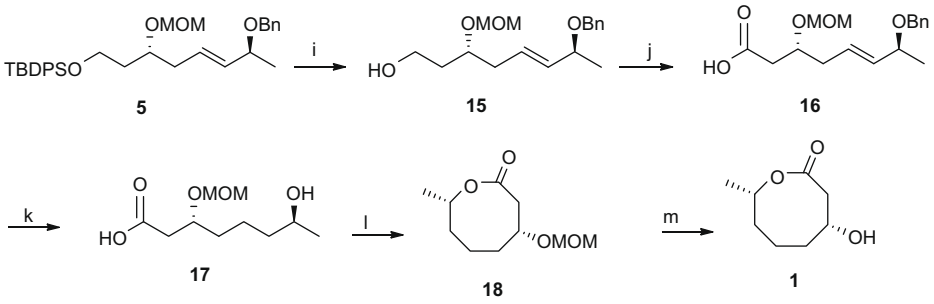
The key fragment **5** can also be synthesized from the protected homoallyl alcohol **14** and hence this provides access to target compound. Grubb's cross metathesis reaction of **7** with methyl vinyl ketone (2 equiv) led to the α,β-unsaturated ketone **15** in 81% yield.[15] In our laboratory, we had previously demonstrated the oxazaborolidine catalyst for applications in reduction reactions.[7c] To our delight, the use of this catalyst with BH_3·DMS at −40 °C in



Scheme 3. Reagents and conditions: (d) TBDPSCl, DIPEA, CH_2Cl_2, 0 °C to rt, 2 h, 95%; (e) IBX, DMSO, THF, rt, 1 h, 92%; (f) (*R,R*)-**I** (10 mol %), $Bu_3SnCH_2CH{=}CH_2$, CH_2Cl_2, −15 °C to 0 °C, 24 h, 86%; (g) MOMCl, DIPEA, CH_2Cl_2 0 °C to rt, 7 h, 90%; (h) compound **6** (2 equiv), 5 mol % Grubb's second generation catalyst, CH_2Cl_2, reflux, 6 h, 80%.



Scheme 4. Reagents and conditions: (a) Methyl vinyl ketone (2 equiv), 5 mol % Grubb's **II**, CH_2Cl_2, reflux, 6 h, 81%; (b) R-CBS catalyst, THF, −40 °C, BH_3·DMS, 3 h, 90%, 97% de; (c) NaH, BnBr, THF, 0 °C to rt, 3 h, 95%.



Scheme 5. Reagents and conditions: (i) TBAF, THF, rt, 10 h, 91%; (j)TEMPO, BAIB, CH_2Cl_2–H_2O (1:1), rt, 94%; (k) H_2, Pd/C, EtOAc, rt, 12 h, 90%; (l) DIPEA, 2,4,6-$Cl_3C_6H_2COCl$, DMAP, PhH, 80 °C, 68%; (m) 4 N HCl, THF, 0 °C, 1 h, 85%.

the reduction[16] of **15** furnished allyl alcohol **16** with an (*S*)-configuration in 90% yield with 97% de.[17] This presumably arises from the 'diastereo selective' reduction (as opposed to the over-reduction) of **16** to the allyl alcohol, which spontaneously directs to form the 1**6** as a single diastereomer. The resultant allylalcohol **16** protected as its benzyl ether using BnBr and NaH in THF to afford the fragment **5** in 95% yield (Scheme 4).

With the successful synthesis of the key fragment **5**, we proceeded to macrolactonization via Yamaguchi lactonization as depicted in Scheme 5. Thus, removal of the TBDPS group with TBAF followed by the oxidation (TEMPO, BAIB in DCM and water in 1:1 ratio) smoothly furnished acid **17** in 94% yield.[18] Double bond reduction followed by deprotection of benzyl group was accomplished by hydrogenation[19] employing 10% Pd/C in ethyl acetate to give alcohol **4** in 90% yield, which was then subjected to macrolactonization by using the Yamaguchi procedure to provide eight-membered macrolactone **18**. Finally, removal of the MOM group[20] in **18** with 4 N HCl in THF furnished the (+)-cephalosporolide D (**1**) in 80% yield.

All the intermediate compounds including the cephalosporolide D were fully characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data.[21] Comparison of our physical and spectroscopic data with the published data[3b] confirmed our successful synthesis of (+)-cephalosporolide D ($[\alpha]_D^{25}$ + 45.2 (*c* 0.5, $CHCl_3$); lit. [1] $[\alpha]_D^{25}$ + 47.5 (*c* 0.2, $CHCl_3$)).

In conclusion, we have developed an efficient stereoselective protocol for the synthesis of cephalosporolide D (**1**) by employing Maruoka asymmetric allylation, and Grubbs cross metathesis reaction and Yamaguchi lactonization as the key reaction steps. We believe that the presented synthetic method could be of value in the development of novel eight-membered lactone ring-based analogues for cephalosporolide research.

Acknowledgements

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References and notes

1. For a recent review, see: Rosseau, G. *Tetrahedron* **1995**, *51*, 2777.
2. Ackland, M. J.; Hanson, J. R.; Hitchcock; Ratcliffe, A. H. *J. Chem. Soc., Perkin. Trans 1* **1985**, 843.
3. (a) Shiina, I.; Hashizume, M.; Yamai, Y.; Oshiumi, H.; Shimazaki, T.; Takasuma, Y.; Ibuka, R. *Tetrahedron Lett.* **2004**, *45*, 543; (b) Buszek, K. R.; Jeong, Y.; Sato, N.; Still, P. C.; Muino, P. L.; Ghosh, I. *Synth. Commun.* **2001**, *31*, 1781.
4. Shiina, I.; Hashizume, M.; Yamai, Y.; Oshiumi, H.; Shimazaki, T.; Takasuma, Y.; Ibuka, R. *Chem. Eur. J.* **2005**, *11*, 6601.
5. (a) Shiina, I.; Fukuda, Y.; Ishii, T.; Fujisawa, H.; Mukaiyama, T. *Chem. Lett.* **1998**, 831; (b) Shiina, I.; Fujisawa, H.; Ishii, T.; Fukuda, Y. *Heterocycles* **2000**, *52*, 1105.
6. Shiina, I. *Chem. Rev.* **2007**, *107*, 239.
7. (a) Kumar, R. S. C.; Sreedhar, E.; Reddy, G. V.; Babu, K. S.; Rao, J. M. *Tetrahedron: Asymmetry* **2009**, *20*, 1160; (b) Sreedhar, E.; Kumar, R. S. C.; Reddy, G. V.; Robinson, A.; Babu, K. S.; Rao, J. M. *Tetrahedron: Asymmetry* **2009**, *20*, 440; (c) Reddy, G. V.; Kumar, R. S. C.; Babu, K. S.; Rao, J. M. *Tetrahedron Lett.* **2009**, *50*, 4117; (d) Kumar, R. S. C.; Reddy, G. V.; Shankariah, G.; Babu, K. S.; Rao, J. M. *Tetrahedron Lett.* **2010**, *51*, 1114.
8. Inanaga, J.; Harata, K.; Saeki, H.; Katsaki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
9. Solladle-Cavallo, A.; Bonne, F. *Tetrahedron: Asymmetry* **1996**, *7*, 171.
10. Freeman, F.; Kim, D. S. H. L. *J. Org. Chem.* **1992**, *57*, 1722.
11. Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, *35*, 8019.
12. (a) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708; (b) Chandrasekhar, S.; Narsihmulu, Ch.; Sultana, S. S.; Reddy, M. S. *Tetrahedron Lett.* **2004**, *45*, 9299.
13. The enantiomeric excess (ee) of the homoallyl alcohol **14** was determined by HPLC [Diacel OD-H column, 250 × 4.6 mm, 5 μ, 254 nm; eluent, 2% (0.1% of DMA) ethanol, 98% hexane, 20 μL injection volume, flow rate 0.5 mL/min retention time 9.39 and 10.46 min].
14. Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.
15. BouzBouz, S.; Simmons, R.; Cossy, J. *Org. Lett.* **2004**, *6*, 3465. and references cited therein.
16. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; (b) Corey, J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.
17. The diastereoselectivity was determined by HPLC [Diacel OD-H column, 250 × 4.6 mm, 5 μ, 225 and 254 nm; eluent, 5% (0.1% of DMA) ethanol, 95% hexane, 20 μL injection volume, flow rate 1 mL/min retention time 3.1 and 4.3 min].
18. (a) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974; (b) Epp, J. B.; Widlanski, T. S. *J. Org. Chem.* **1999**, *64*, 293.
19. McNeill, A. H.; Thomas, E. J. *Tetrahedron Lett.* **1993**, *34*, 1669.
20. Meyers, A. I.; Durandetta, J. L.; Munavu, R. *J. Org. Chem.* **1975**, *40*, 2025.
21. *Spectral Data for selected compounds*:
Compound **6**: oil, $[\alpha]_D^{25}$ −25 (*c* 1, $CHCl_3$); IR (KBr): 2976, 2859, 1446, 1090, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32–7.28 (m, 5H), 5.83–5.70 (m, 1H), 5.23–5.12 (m, 2H), 4.59–4.32 (m, 2H), 3.94–3.84 (m,1H), 1.28 (d, 3H, *J* = 6.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 139.9, 138.5, 127.8, 127.0, 126.8, 115.5, 75.7, 69.4, 21.1; HRESIMS *m*/*z* $[M+Na]^+$; calcd for $C_{11}H_{14}NaO$: 185.0942, found: 185.0939.
Compound **7**: oil, $[\alpha]_D^{25}$ −1.8 (*c* 1, $CHCl_3$); IR (KBr): 3070, 2933, 2888, 1467, 1106, 702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64–7.51 (m, 4H), 7.35–7.20 (m, 6H), 5.80–5.60 (m, 1H), 5.01–4.90 (m, 2H), 4.53 (s, 2H), 3.83–3.58 (m, 3H), 3.21 (s, 3H), 2.25–2.15 (m, 2H), 1.71–1.58 (m, 2H), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.43, 134.54, 133.74, 129.52, 127.56, 117.12, 95.60, 73.90, 60.37, 55.37, 39.20, 37.08, 26.79, 19.12; HRESIMS *m*/*z* $[M+Na]^+$; calcd for

$C_{24}H_{34}NaO_3Si$: 421.2175; found: 421.2164.

Compound **5**: $[\alpha]_D^{25}$ −17.4 (*c* 1, $CHCl_3$); IR (KBr): 2930, 2856, 1427, 1110, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.76–7.48 (m, 4H), 7.35–7.05 (m, 11H), 5.58–5.24 (m, 2H), 4.54–4.37 (m, 3H), 4.29–4.13 (m, 1H), 3.83–3.54 (m, 3H), 3.17 (s, 3H), 2.41–2.34 (m, 2H), 1.69–1.53(m, 2H), 1.15 (d, 3H, *J* = 6.42 Hz), 0.96 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.8, 135.5, 134.8, 133.7, 129.6, 129.5, 128.6, 128.2, 127.6, 127.3, 95.5, 75.5, 74.1, 69.6, 60.4, 55.3, 37.67, 26.69, 21.8, 19.2; HRESIMS *m*/*z* $[M+NH_4]^+$; calcd for $C_{33}H_{48}NO_4Si$: 550.3353; found: 550.3351.

Compound **17**: $[\alpha]_D^{25}$ +1.7 (*c* 1, $CHCl_3$); IR (KBr): 3462, 2923, 2852, 1715, 1038 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.65–4.51 (m, 2H), 3.96–3.84 (m, 1H), 3.80–3.65 (m, 1H), 3.29 (s, 3H), 2.60–2.32 (m, 2H), 1.44–1.32 (m, 4H), 1.23–1.15 (m, 2H), 1.12 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.2, 95.96, 74.6, 67.7, 55.5, 38.9, 34.7, 29.7, 23.5, 21.3; HRESIMS m/z $[M+Na]^+$; calcd for $C_{10}H_{20}NaO_5$: 243.1208; found: 243.1200.