Tetrahedron Letters 53 (2012) 1186–1189

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Total synthesis of stagonolide B

Tapas Das, Tridib Mahapatra, Samik Nanda *

Department of Chemistry, Indian Institute of Technology, Kharagpur 721302, India

ARTICLE INFO

Article history:
Received 10 December 2011
Revised 26 December 2011
Accepted 27 December 2011
Available online 3 January 2012

Keywords:
Small ring macrolide
Enzymatic hydrocynation
Asymmetric allylation
Cross metathesis
Macrolactonization

ABSTRACT

Asymmetric total synthesis of nonenolide stagonolide-B has been presented in this Letter. The main highlight of our synthetic strategy is the application of hydroxynitrile lyase (*ParsHNL*) mediated asymmetric synthesis of cyanohydrin, Sharpless asymmetric dihydroxylation, cross metathesis (CM) reaction, stereoselective Keck allylation reaction and Yamaguchi macrolactonization at a late stage enables us to achieve the synthesis of the target molecule in an efficient way.

Stagonolides are a class of naturally occurring nonenolides isolated from a fungal pathogen *Stagonospora cirsii*. These small ring macrolides possess interesting biological activities (mainly phytotoxic). In a preliminary study, it was observed that *S. cirsii* is capable of producing phytotoxic metabolites, because isolated culture filtrates demonstrated phytotoxic activity. Five new nonenolides, named stagonolides B–F, were isolated and characterized using spectroscopic methods.[1] Further four nonenolides were isolated later on and characterized by spectroscopy. Three were new compounds named stagonolides G–I, and the fourth was identified as modiolide A, previously isolated from *Paraphaeosphaeria* sp., a fungus separated from the horse mussel (Fig. 1).[2] In our continuous effort toward the synthetic studies of the small ring macrolides, we have already reported the total synthesis of stagonolide C,[3] stagonolide D & G,[4] stagonolide-E,[5] chloriolide,[6] and achaetolide.[7] The main highlight of our previous synthetic strategy was chemoenzymatic kinetic resolution coupled with Mitsunobu inversion and chemoenzymatic dynamic kinetic resolution to access some valuable chiral secondary alcohol intermediates. These intermediates are then employed successively to gain access of more advanced intermediates which have close resemblance to the target molecule. In the final step of synthesis we often apply RCM reaction by Grubbs catalyst as well as several macrolactonization protocols. The success of our synthetic strategy depends on the optimization of RCM method and macrolactonization protocol.

Till today three asymmetric syntheses of stagonolide-B are reported in the literature.[8,9] All the synthetic strategies involve the successful application of RCM (ring closing metathesis) reaction at late stage with Grubbs olefin metathesis catalyst.[10] In this Letter we would like to report our synthetic strategies for the asymmetric total synthesis of stagonolide-B by the successful application of Yamaguchi macrolactonization. Our retrosynthetic analysis of stagonolide-B is presented in Scheme 1.

We have planned to adopt a Yamaguchi macrolactonization[11] at the penultimate step from the properly substituted seco acid (**2**), which in turn can be accessed from intermediate **3** by asymmetric catalytic allylation reaction.[12] Cross metathesis reaction was thought to be applied to construct the C6–C7 olefinic unsaturation from the intermediate **4**.[13] The intermediate **4** can be achieved from (*Z*)-ester **5** by asymmetric dihydroxylation reaction.[14] Ester **5** can be prepared from aldehyde **7**, synthesized by *ParsHNL* catalyzed hydrocyanation reaction (Scheme 2).

We have started our synthetic journey from the commercially available *n*-butanal. Asymmetric hydrocyanation reaction with *Prunus armeniaca* hydroxynitrile lyase (*ParsHNL*) and HCN in DIPE (diisopropyl ether) solvent afforded the corresponding (*R*)-cyanohydrin in a 92% yield (ee = 96%).[15] The enzymatic hydrocyanation with hydroxynitrile lyase is a well documented strategy for the asymmetric synthesis of cyanohydrins, and we have explored the methodology extensively in our group by using a (*R*)-HNL (*hydroxynitrile lyase* from *Prunus armeniaca*) from Himalayan apricot (*Prunus armeniaca*, Shakarpara cultivar).[16] The reaction is very efficient in terms of chemical yield as well as excellent enantioselection in the product cyanohydrins. The secondary hydroxyl group in (*R*)-**6** is protected as its TBDPS ether by treatment with TBDPS-Cl and imidazole followed by treatment with DIBAL-H at −78 °C afforded the aldehyde **7** in a 72% yield (two steps). *cis*-Selective HWE (Horner–Wadsworth–Emmons) olefination reaction by Ando protocol[17] yielded

* Corresponding author. Tel: +91 3222 283328; fax: +91 3222 282252.
E-mail address: snanda@chem.iitkgp.ernet.in (S. Nanda).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.12.119

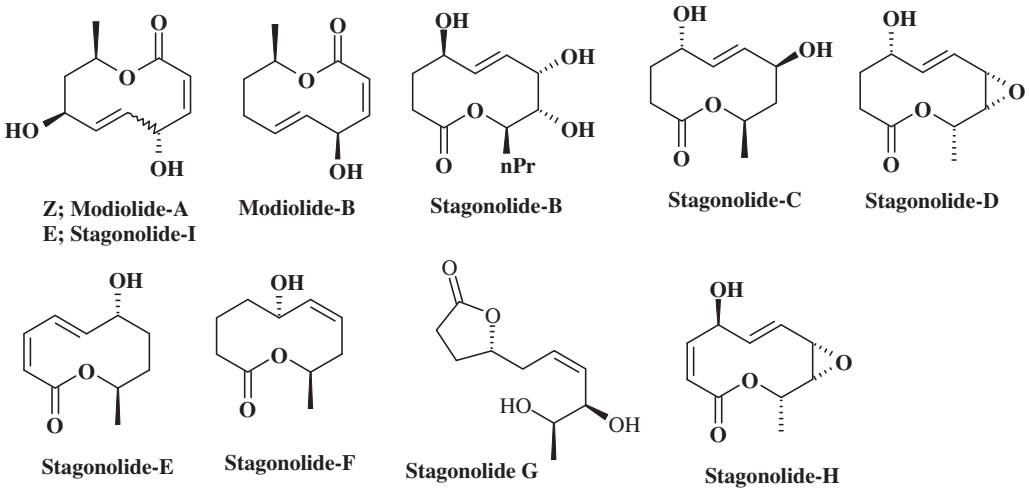
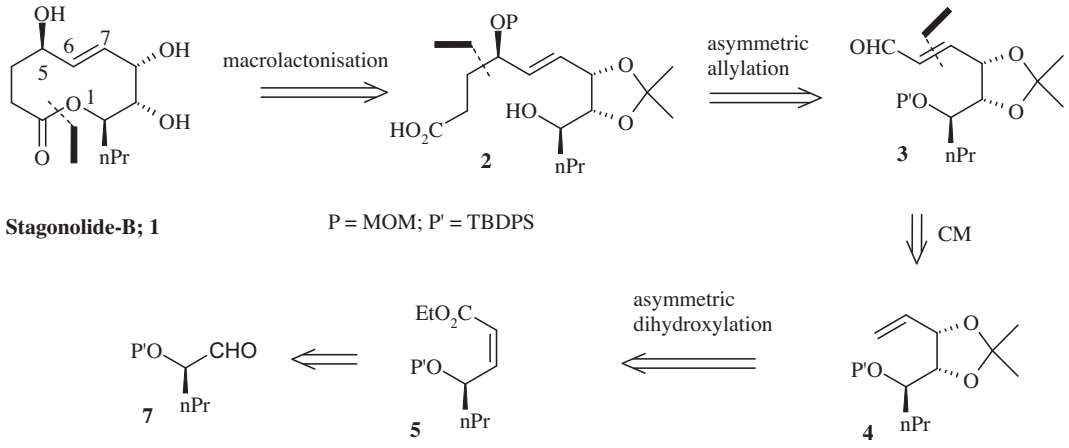


Figure 1. Naturally occurring stagonolides.



Scheme 1. Retrosynthetic analysis of stagonolide-B.

the *Z*-olefin **5** in an 82% yield.[18] Asymmetric dihydroxylation reaction of olefin **5** with ADmix-β afforded the diol **8** in a 79% yield.[19] The diol **8** is protected as its acetonide **9**, by treatment with 2,2-DMP (2,2-dimethoxypropane) in an 87% yield. The ester functionality in compound **9** was reduced with DIBAL-H to afford aldehyde **10** in an 82% yield. Wittig olefination with triphenylphosphoniummethyl iodide in the presence of LHMDS at 0 °C afforded the olefin **4** in an 80% yield. Cross metathesis reaction with freshly distilled acrolein in the presence of Hoveyda–Grubbs metathesis catalyst (HG-II, 5 mol %) afforded the unsaturated aldehyde (exclusively *E*) **3** in an 85% yield.[20] Catalytic asymmetric allylation under Keck condition with allyltributylstanane and (*R*)-BINOL afforded compound **11** in a 76% yield.[21] The secondary hydroxyl group is protected as its MOM ether[22] by treatment with MOM-Cl and DIPEA to yield **12** in an 88% yield. Regioselective hydroboration with BH_3/SMe_2 yielded the alcohol **13** (72%). PDC oxidation[23] of alcohol **13** afforded the carboxylic acid **14** in a 78% yield. Deprotection of the TBDPS group is achieved by treating **14** with TBAF to afford the seco acid **2** in an 88% yield. The crude seco acid is subjected to macrolactonization reaction under Yamaguchi condition to afford the cyclized lactone product **15** in a 62% yield.[24] Finally deprotection of the MOM group is achieved by treating compound **15** in presence of PTSA in DCM to afford stagonolide-B (**1**) in an 80% yield (overall yield = 4.2% from *n*-butanal; Scheme 2). The spectral characteristic values (^1H & ^{13}C NMR) of our synthesized stagonolide-B match perfectly with the natural stagonolide-B.[2,7]

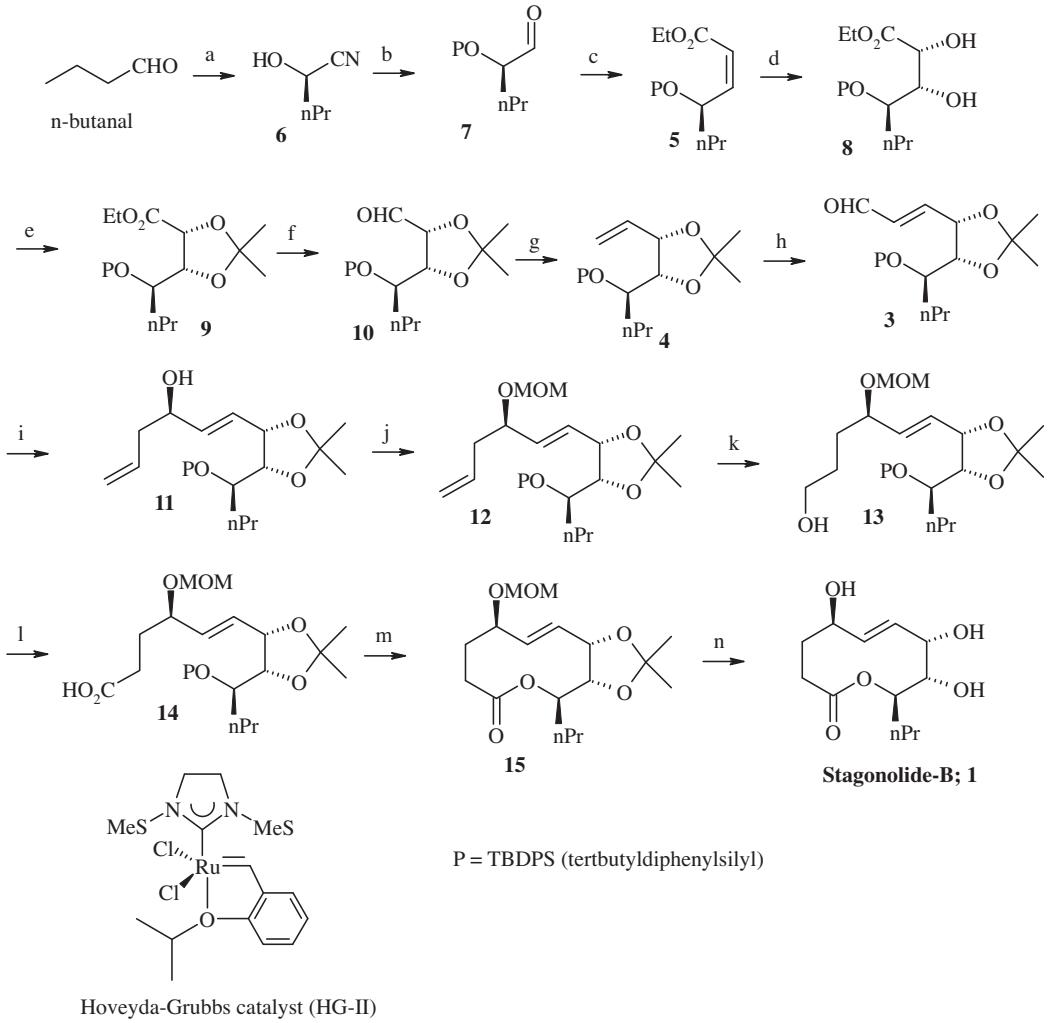
In conclusion an efficient chemoenzymatic asymmetric synthesis of the target molecule stagonolide-B has been accomplished in a linear way. The main highlights of our synthetic strategy involves the application of hydroxynitrile lyase mediated asymmetric cyanohydrin synthesis, asymmetric dihydroxylation reaction, stereoselective cross metathesis reaction, catalytic asymmetric allylation, and finally macrolactonization of properly functionalized hydroxyl acids yields the target molecule in an efficient way.

Acknowledgments

We are thankful to CSIR (New Delhi, India; Grant No: 01-2109/07/EMR-II) and DBT (New Delhi, India; Grant No: BT/PR13830/PID/06/568/2010) for financial support and DST (New Delhi, India) for NMR facility at our institute. Two of the authors (T.D. and T.M.) are thankful to CSIR for senior research fellowship.

Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra for all new compounds are available) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.12.119.



Scheme 2. Asymmetric synthesis of stagonolide-B. Reagents and conditions: (a) *ParsHNL* (*Prunus armeniaca* hydroxynitrile lyase), HCN, DIPE, citrate buffer (pH = 4.0), 6 h, 92%; (b) (i) Imidazole, TBDPS-Cl, DMAP (cat), 12 h, 88%; (ii) DIBAL-H, DCM, −78 °C, 82%; (c) $(PhO)_2POCH_2CO_2Et$, NaH, 0 °C, 82%; (d) AD mix-β, *t*-BuOH–H_2O (4:1), $MeSO_2NH_2$; 79%; (e) 2,2-DMP, CSA, 87%; (f) DIBAL-H, DCM, −78 °C, 82%; (g) LHMDS, PH_3P^+MeI, 0 °C, 1 h, 80%; (h) HG-II (5 mol %), acrolein, reflux, DCM, 6 h, 85%; (i) (*R*)-BINOL, Ti(OiPr)4, allyl tributylstanane, DCM, −20 °C, 80 h, 76%; (j) MOM-Cl, DIPEA, rt, 12 h, 88%; (k) BH_3:Me_2S, THF, NaOH, H_2O_2, 3 h, 72%; (l) PDC, DMF, 6 h, 78%; (m) (i) TBAF, THF, rt, 3 h, 88%; (ii) 2,4,6-trichlorobenzoylchloride, DIPEA (diisopropylethyl amine), DMAP, toluene 60 °C, 24 h, 62%; (n) PTSA, DCM, 12 h, 80%.

References and notes

1. Evidente, A.; Capasso, R.; Andolfi, A.; Vurro, M.; Chiara Zonno, M. *Nat. Toxins* **1999**, *6*, 183.
2. (a) Evidente, A.; Cimmino, A.; Berestetskiy, A.; Mitina, G.; Andolfi, A.; Motta, A. *J. Nat. Prod.* **2008**, *71*, 31; (b) Evidente, A.; Cimmino, A.; Berestetskiy, A.; Andolfi, A.; Motta, A. *J. Nat. Prod.* **2008**, *71*, 1897; (c) Greve, H.; Schupp, P. J.; Eguereva, E.; Kehraus, S.; Konig, G. M. *J. Nat. Prod.* **2008**, *71*, 1651.
3. Jana, N.; Mahapatra, T.; Nanda, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2622.
4. Mahapatra, T.; Das, T.; Nanda, S. *Bull. Chem. Soc. Jpn.* **2011**, *84*, 511.
5. Das, T.; Nanda, S. *Tetrahedron Lett.* **2012**, *53*, 256.
6. Das, T.; Jana, N.; Nanda, S. *Tetrahedron Lett.* **2010**, *51*, 2644.
7. Das, T.; Bhuniya, R.; Nanda, S. *Tetrahedron: Asymmetry* **2010**, *21*, 2206.
8. (a) Srihari, P.; Kumaraswamy, B.; Somaiah, R.; Yadav, J. S. *Synthesis* **2010**, 1039; (b) Prabhakar, P.; Rajaram, S.; Kumar Reddy, D.; Shekar, V.; Venkateswarlu, Y. *Tetrahedron: Asymmetry* **2010**, *21*, 216; (c) Giri, A. G.; Mondal, M. A.; Puranik, V. G.; Ramana, C. V. *Org. Biomol. Chem* **2010**, *8*, 398.
9. For total synthesis of stagonolides and related molecules from other groups see: (a) Srihari, P.; Maheswara Rao, G.; Srinivasa Rao, R.; Yadav, J. S. *Synthesis* **2010**, 2407; (b) Mohapatra, D. K.; Somaiah, R.; Rao, M. M.; Caijo, F.; Mauduit, M.; Yadav, J. S. *Synlett* **2010**, 1223; (c) Mohapatra, D. K.; Dash, U.; Naidu, R. P.; Yadav, J. S. *Synlett* **2009**, 2129; (d) Srihari, P.; Kumaraswamy, B.; Maheswara Rao, G.; Yadav, J. S. *Tetrahedron: Asymmetry* **2010**, *21*, 106; (e) Perepogu, A. K.; Raman, D.; Murty, U. S. N.; Rao, V. *J. Biorg. Chem.* **2009**, *37*, 46; (f) Giri, A. G.; Mondal, M. A.; Puranik, V. G.; Ramana, C. V. *Org. Biomol. Chem.* **2010**, *8*, 398; (g) Srihari, P.; Kumaraswamy, B.; Shankar, P.; Ravishashidhar, V.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 6174; (h) Srihari, P.; Kumaraswamy, B.; Bhunia, D. C.; Yadav, J. S. *Tetrahedron Lett.* **2010**, *51*, 2903; (i) Angulo-Pachon, C. A.; Diaz-Oitra, S.; Murga, J.; Carda, M.; Marco, J. A. *Org. Lett.* **2010**, *12*, 5752; (j) Kumar, C. N. S. S.; Ravinder, M.; Kumar, S. N.; Rao, V. J. *Synthesis* **2011**, 451–458; (k) Chandrasekhar, S.; Balaji, S. V.; Rajesj, G. *Tetrahedron Lett.* **2010**, *51*, 5164; (l) Rao, K. S.; Chatttapadhyay, A.; Ghosh, S. *Synlett* **2010**, 3078; (m) Sabitha, G.; Srinivas, R.; Yadav, J. S. *Synthesis* **2011**, 3343.
10. Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc* **1996**, *118*, 100.
11. Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.
12. Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467.
13. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
14. Tietze, L. F.; Eicher, T.; Diederichsen, U.; Speicher, A. In *Reactions and Syntheses*; Wiley-VCH: Weinheim, 2007; p 211.
15. (a)Bhunya, R.; Jana, N.; Das, T.; Nanda, S. *Syn Lett*, **2009**, 1237–1240. (b) Bhunya, R.; Mahapatra, T.; Nanda, S. *Tetrahedron : Asymmetry*, **2009**, *20*, 1526–1530.

*(R)-2-Hydroxypentanenitrile (**6**)*: To a solution of *n*-butanal (7.2 g, 0.1 mol) in DIPE (60 ml), a solution of *ParsHNL* (300 IU/10 mmol of aldehyde, approximately 10 ml of crude enzyme solution) was added and the resulting mixture was stirred vigorously until an emulsion was formed. The pH of the enzyme solution was previously adjusted to 4.0 with 10% citric acid solution. Freshly prepared HCN in DIPE (2 equiv) was added to it, and the temperature of the solution was kept at 10 °C. After completion of the reaction it was extracted thoroughly with ether several times and the organic layer was dried (Na_2SO_4). Evaporation of the solvent yielded the crude cyanohydrin which was purified by chromatography.

Preparation of HCN in DIPE: NaCN (10 g) and citric acid (0.1 g) were dissolved in water (100 mL). The solution was cooled in an ice/water bath and extracted with DIPE (50 mL), while acidifying with 33% HCl until pH 5.5. The water layer,

which contained a suspension of NaCl, was extracted twice with DIPE (25 mL). The combined DIPE layers were stored in a dark bottle. The above procedure must be performed in a well ventilated fume hood with proper glass ware and hand wares (gloves).

16. The enantiomeric excess (ee) of the hydrocyanation reaction was determined with the help of chiral HPLC analysis of the corresponding benzoate derivative (Chiralpak AD-H; hexane: isopropanol = 19:1; flow rate 0.9 ml/min; t_{major} = 6.8 min; t_{minor} = 7.2 min).
17. Ando, K. *J. Org. Chem.* **1997**, *62*, 1934.
18. *(R,Z)-ethyl 4-(tert-butyldiphenylsilyloxy)hept-2-enoate (compound **5**)*: To a solution of Ethyl (diphenylphosphono) acetate (3.7 g, 11.76 mmol) in THF (45 ml) was added NaH (60%) ((470.4 mg, 11.76 mmol) at 0 °C; 15 min later, aldehyde **7** (4.0 g, 11.76 mmol) in THF (10 ml) was added, and the resulting mixture was gradually warmed to the room temperature over 1.2 h. After that time water was added to it, extracted with ethyl acetate and brine. The organic extract was dried over $MgSO_4$ and evaporated to yielded the crude olefin (*Z*/*E* = 95:5) which was separated by flash chromatography to afford ester **5** in 82% yield.
19. *(2R,3S,4R)-ethyl 4-(tert-butyldiphenylsilyloxy)-2,3-dihydroxyheptanoate (compound 8)*: *t*-BuOH (29 ml), H_2O (29 ml) and AD-mix β (11.6 g) were mixed and the mixture was stirred for 15 min. Methanesulfonamide (1.1 g) was then added and the stirring was continued for a further 15 min. Ester compound **5** (3.5 g, 8.53 mmol) was then added and the slurry was stirred vigorously at 20 °C for 24 h, sodium sulfite (15 g) was added and stirring was continued for further 1 h. The reaction mixture was extracted with EtOAc, the organic layer was dried over Na_2SO_4 and evaporated in vacuo. The diol was purified by flash chromatography (1:3; EtOAc–hexane) to afford (79%) of the diol **8** as a single isolable product.
20. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.*, **2000**, *122*, 8168.
*(E)-3-((4S,5S)-5-((R)-1-(tert-butyldiphenylsilyloxy)butyl)-2,2-dimethyl-1,3-dioxolan-4-yl) acrylaldehyde (compound **3**)*: A flame-dried round-bottom flask was charged with olefin **4** (2.5 g 5.7 mmol), freshly distilled acrolein (0.578 ml, 8.66 mmol) and dicholoromethane (25 ml). Hoveyda–Grubbs catalyst (HG-II, 5 mol %) was subsequently added as a solid, producing a light green solution which was refluxed for 6 h. The mixture was then concentrated in vacuo to a dark brown oil. Purification of this residue on silica gel by flash chromatography (pet ether/ethyl acetate: 1/10) affords aldehyde **3** as a yellow oil with 85% yield.
21. Keck, G. E.; Truong, A. P. *Org. Lett.*, **2005,** *7*, 2149.
*(R,E)-1-((4S,5S)-5-((R)-1-(tert-butyldiphenylsilyloxy) butyl)-2,2-dimethyl-1,3-dioxolan-4-yl)hexa-1,5-dien-3-ol (compound **11**)*: A mixture of (*R*)-BINOL (60.3 mg, 0.21 mmol), 1 M $Ti(O\text{-}i\text{-}pr)_4$ in DCM (0.21 ml, 0.21 mmol), and oven-dried powdered 4-A sieves in DCM was heated at reflux for 1 h. The red-brown mixture was cooled to room temperature and aldehyde **3** (1 g, 2.1 mmol) was added. After being stirred for 10 min, the contents were cooled to −78 °C, and allyltri-*n*-butylstannane (772.4 mg, 2.33 mmol) was added. The reaction was stirred for 10 min and then placed in a preset reaction chamber at −20 °C for 80 h. Saturated $NaHCO_3$ (0.7 ml) was added, and the contents were stirred for 1 h and then poured over Na_2SO_4 and filtered through celite. The crude mixture was purified by flash chromatography (pet ether/ethyl acetate: 5:1) afforded the compound **11** with 76% yield. Formation of a minor diastereomer was indicated in TLC and was separated by chromatography (de = 19:1).
22. Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.
23. Chen, J.; Li, Y.; Cao, X. *Tetrahedron: Asymmetry* **2006**, *17*, 933.
24. *(3aR,4S,9R,11aS,E)-9-(methoxymethoxy)-2,2-dimethyl-4-propyl-4,5,8,9-tetrahydrocyclodeca[d][1,3]dioxol-6(3aH,7H,11aH)-one (compound **15**)*: Compound **14** (125 mg, 0.21 mmol) was taken in dry THF (2 ml). TBAF (1 M in THF, 0.42 ml) was added to it, and the reaction mixture was stirred for 3 h at room temperature. After that time, THF was evaporated and water (4 ml) was added to it. The reaction mixture was extracted with EtOAc (50 ml). The organic layer was washed with $NaHCO_3$ and brine, dried over Na_2SO_4, purified by flash chromatography (5:1; hexane–EtOAc) to afford 40 mg hydroxy acid in a 50% yield.
To a solution of hydroxy acid (40 mg, 0.11 mmol) in dry toluene (10 ml) were added 2,4,6-trichlorobenzoyl chloride (0.4 ml, 2.3 mmol) and diisopropyl ethyl amine (0.8 ml) at 23 °C. The resulting mixture was stirred for 15 h at the same temperature. The solution was diluted by the addition of dry tolune (10 ml) and was added by syringe pump slowly to a solution of DMAP (240 mg, 2.76 mmol) in dry tolune (200 ml) at 60 °C over 10 h. The reaction was stirred for an additional 24 h at the same temperature and quenched by adding saturated aqueous NH_4Cl solution, extracted by ethyl acetate, dried, concentrated, and purified by column chromatography (pet ether/ethyl acetate: 20/1) afforded the lactone **15** in a 62% yield.