Tetrahedron 70 (2014) 2634–2642

Contents lists available at ScienceDirect

Tetrahedron

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

Asymmetric synthesis of naturally occurring nonenolide xyolide through cross metathesis and macrolactonization reaction

Rohan Kalyan Rej, Anuvab Jana, Samik Nanda *

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

ARTICLE INFO

Article history:
Received 22 January 2014
Received in revised form 15 February 2014
Accepted 24 February 2014
Available online 4 March 2014

ABSTRACT

Asymmetric total synthesis of xyolide, a small ring macrolide is presented in this article. The synthesis is achieved through an '*E*' selective cross metathesis (CM) reaction between two appropriate fragments followed by lactonization by Shiina method. One of the fragments containing 7*S*,8*S*,9*R* stereocenters of xyolide is accessed from *n*-nonanal by adopting an organocatalytic asymmetric α-aminooxylation, *Z*-selective Ando olefination, and substrate directed dihydroxylation reaction. The other fragments containing 4*S* stereocenter was prepared by ME-DKR (metal enzyme combined dynamic kinetic resolution) method.

1. Introduction

The wide and diverse range of secondary metabolites produced by endophytes has been shown to combat pathogens and even cancers in animals including humans.[1] It is speculated that there may be many thousands of endophytes useful to human being, but as there are few researchers working in this field, and since due to deforestation, many useful endophytes might be permanently lost for medicinal use before they are discovered. It has been reasoned that fungal endophytes isolated from tropical plants found in Amazonian forest would be a rich source of several medicinally important secondary metabolites.[2] And this prompted the recent isolation of xyolide a 10 membered ring nonenolide from an Amazonian endophytes *Xylaria feejeensis* by Handelsman et al.[3] The structure of xyolide was characterized through extensive NMR analysis (1-D and 2-D) and the absolute configuration (4*S*,7*S*,8*S*,9*R*) was determined by exciton-coupled circular dichroism measurement. Close structural inspection of xyolide reveals that it contains a 10 membered macrolide core and a C-9 alkyl (other than −Me) appendage as its main structural components. In addition xyolide also contain *syn* vicinal dihydroxy functionality (7*S* and 8*S*) and the hydroxyl group at C-4 position is half esterified with succinic acid. Cytospolides,[4] Herbarumins,[5] Stagonolide-B,[6] Pinolidoxin,[7] Achaetolide,[8] and Seimatopolides (A and B)[9] are few representative examples belong to this family of nonenolides having a C-9 alkyl substitution (Fig. 1) and exhibit significant biological activities, such as antibacterial, antifungal, cytotoxic, and phytotoxic. Xyolide also exhibit significant inhibitory activity against growth of *Pythium ultimum* an oomycete plant pathogen (MIC=425 μM). Oomycetes are lower eukaryotes, which are closely related to the golden-brown algae, and are known to infect major food crops, causing havoc annual losses estimated in billions of dollars worldwide.

Due to its unique structural feature and biological importance xyolide became an instant target for the synthetic organic community, and till today two syntheses are reported for xyolide. Both of the reported synthesis features a late stage '*E*'-selective RCM (ring closing metathesis reaction). The metathesis precursor was assembled by esterification reaction between properly functionalized carboxylic acid and alcohol fragments.[10] In recent times our group is actively engaged in the synthesis of small and medium sized ring macrolides.[11] In continuation to our effort, herein we intend to report the asymmetric total synthesis of xyolide.

2. Result and discussion

We envisioned that CM reaction (cross metathesis)[12] might be an alternative option to construct the '*E*' olefinic unsaturation at the beginning and then macrolactonization by carboxylic acid activation protocol (such as Yamaguchi or Shiina)[13] will enable us to form the decanolide core of the target molecule. The retrosynthetic analysis for xyolide is outlined in Scheme 1. As presented in Scheme 1, we intend to carry out a late stage macrolactonization on the enantiopure seco-acid. The olefinic unsaturation between C-5 and C-6 is planned to be created by a stereoselective CM reaction between two metathesis partners as presented in Scheme 1. One of the fragment containing 4*S* stereocenter of xyolide will be accessed from 1,4-butanediol through a ME-DKR (metal enzyme combined dynamic kinetic resolution strategy),[14] whereas the other fragment consist of 7*S*,8*S*,9*R* stereocenters is thought to be assembled from *n*-

* Corresponding author. E-mail address: snanda@chem.iitkgp.ernet.in (S. Nanda).

0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.02.072

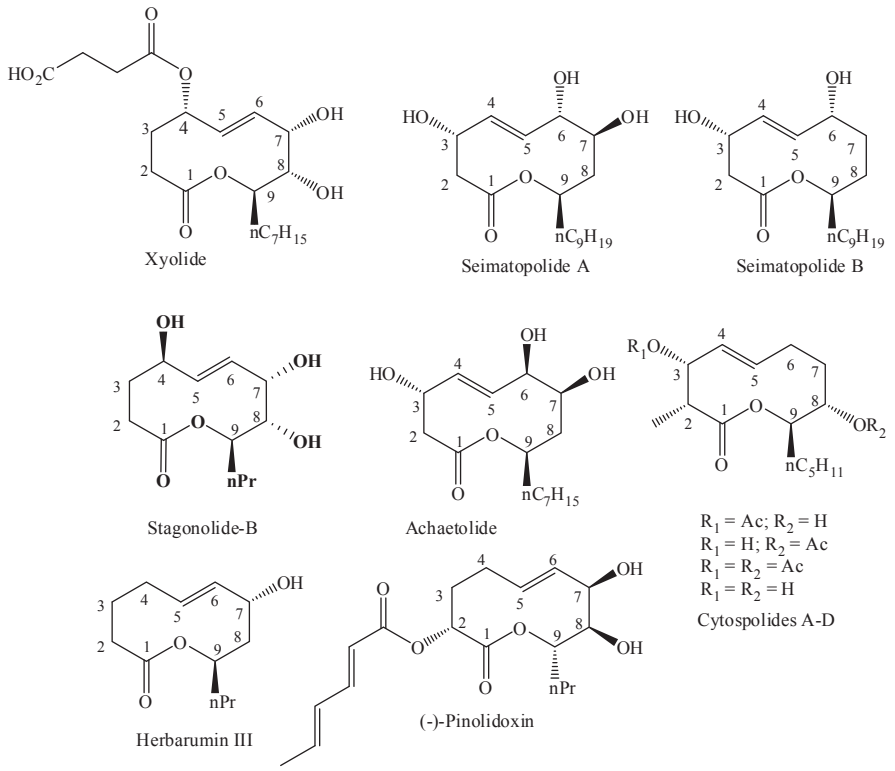
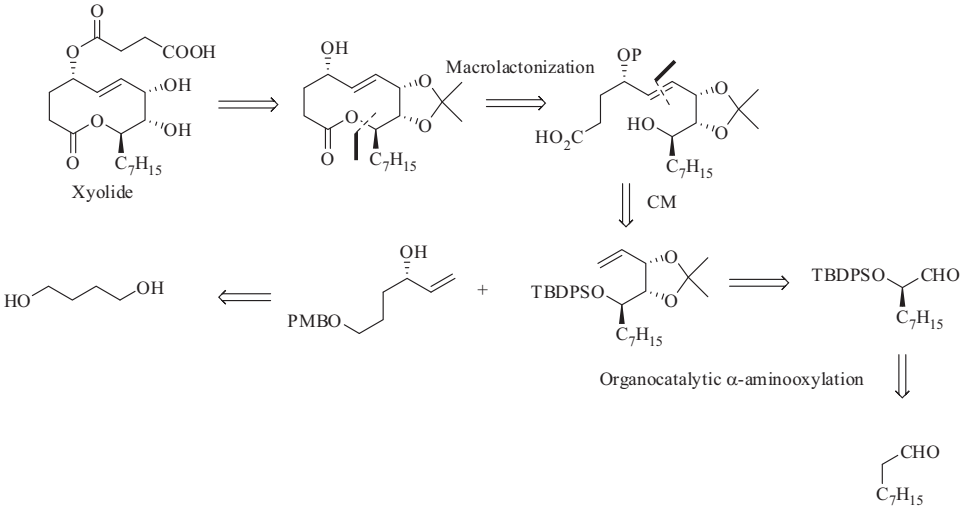


Fig. 1. Few representative nonenolides containing C-9 alkyl substitution (other than Me).

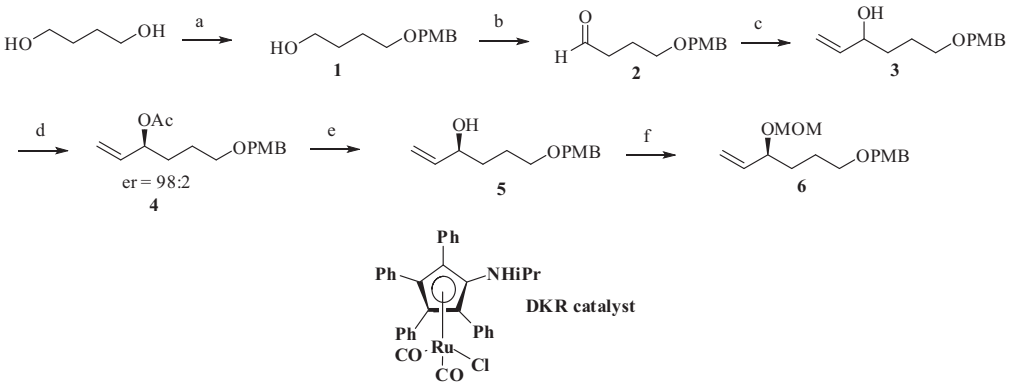


Scheme 1. Retrosynthetic analysis of xyolide.

nonanal through organocatalytic asymmetric α-aminooxylation followed by substrate directed asymmetric dihydroxylation reaction.

2.1. Synthesis of the fragment having 4*S* stereocenter of xyolide

The synthesis begins with 1,4-butanediol, which on selective monoprotection with PMB-Br afforded the corresponding alcohol **1** in 88% yield. Oxidation of alcohol **1** with DMP (Dess Martin periodinane)[15] afforded the corresponding aldehyde **2** in 90% yield. Vinylmagnesium bromide addition to aldehyde **2** at −78 °C furnished racemic compound **3** in 82% yield. ME-DKR of secondary alcohol functionality in compound **3** was achieved by coupling enzyme-catalyzed transesterification reaction with metal-catalyzed (ruthenium based catalyst shown in Scheme 2) racemization method.[16] Isopropenyl acetate was used as the acyl donor in the DKR reaction. The ME-DKR reaction is highly efficient for compound **3** as it yields the corresponding acetate **4** in 90% yield with excellent enantioselection (ee=96%).[17] This kind of ME-DKR reaction is an excellent addition in the toolbox of a synthetic organic chemist as a variety of secondary alcohol containing enantiopure synthons can be accessed by this method. We have already explored this ME-DKR strategy for synthesizing several enantiopure secondary alcohol synthons for the total synthesis of related small ring macrolides.[11d,i] The acetate functionality in compound **4**



Scheme 2. Reagents and conditions: a) NaH, PMB-Br, TBAI, THF, 0 °C—rt, 2 h, 88%; b) DMP, DCM, 0 °C—rt, 1 h, 90%; *c*) CH_2=CHMgBr, THF, −78 °C—rt, 2 h, 82%; d) CAL-B, isopropenyl acetate, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl) ruthenium (II), K_2CO_3, KO^{t}Bu, toluene, 90%; e) K_2CO_3, MeOH, 92%; f) MOM-Cl, DIPEA, DCM, TBAI, rt, 12 h, 90%.

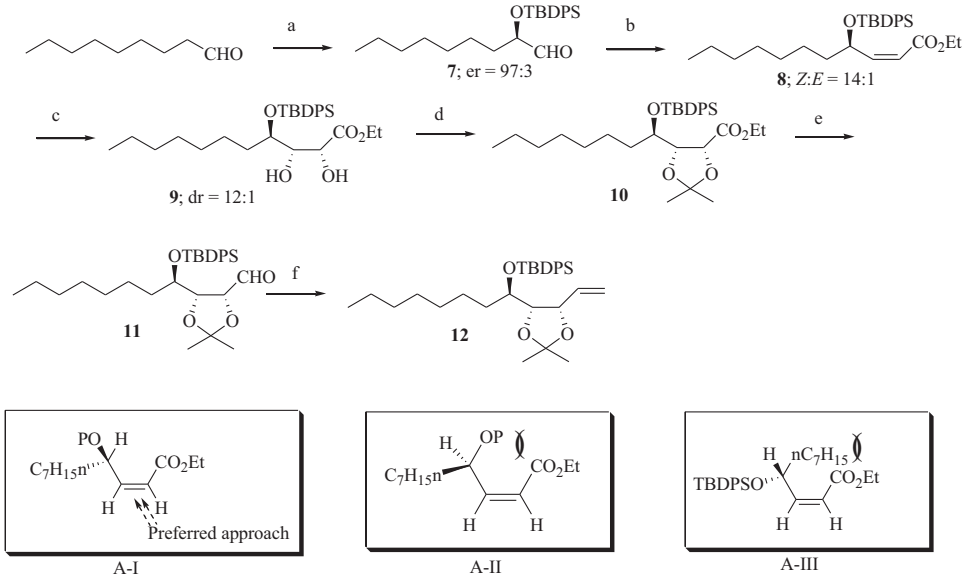
was then removed by treatment with K_2CO_3 in MeOH to yield optically pure **5** in 92% yield. The free alcohol group in compound **5** was protected as its MOM ether by treatment with MOM-Cl to furnish the compound **6** in 90% yield (Scheme 2).

2.2. Synthesis of the fragment having 7*S*,8*S*,9*R* stereocenters of xyolide

The synthesis was initiated from *n*-nonanal, which on organocatalytic asymmetric α-aminooxylation with *S*-proline,[18] followed by cleavage of the O—N bond with $CuSO_4 \cdot 5H_2O$ and subsequent protection of the free hydroxyl group with TBDPS-Cl furnished compound **7** in 80% yield (over three steps). Ando modification[19] of HWE reaction with aldehyde **7** with $(PhO)_2POCH_2CO_2Et$ afforded the corresponding ester **8** in 88% yield (*Z*:*E*=14:1). Next substrate directed dihydroxylation was initiated with compound **8** with OsO_4/NMO in THF:water (3:1) solvent afforded the corresponding diol **9** with good diastereoselection (12:1). The origin of this high selectivity can be explained from Kishi model[20] as shown in Scheme 3. In its ground state compound **8**, might exist as three of the probable conformational isomers, out of which structure A—I is highly probable due to energy considerations, as in the case of other structures due to $A_{1,3}$ strain their relative population will be extremely less. In the structure A—I of compound **8**, as the β-face of the double bond is blocked by bulky TBDPS group (even an electronic repulsion between Os=O bond and the ether oxygen of the —OTBDPS group cannot be ruled out) hence the dihydroxylation selectively occurs from the α-face to afford compound **9** in 90% yield. The diol functionality is now protected as its acetonide upon treatment with 2,2-DMP to furnish compound **10** in 88% yield. Partial reduction with DIBAL-H of compound **10** afforded the aldehyde **11** in 76% yield. Wittig olefination with $Ph_3P^+CH_3I^-$ afforded the olefin **12** in 80% yield (Scheme 3).

2.3. Fragment coupling by CM and completion of the synthesis

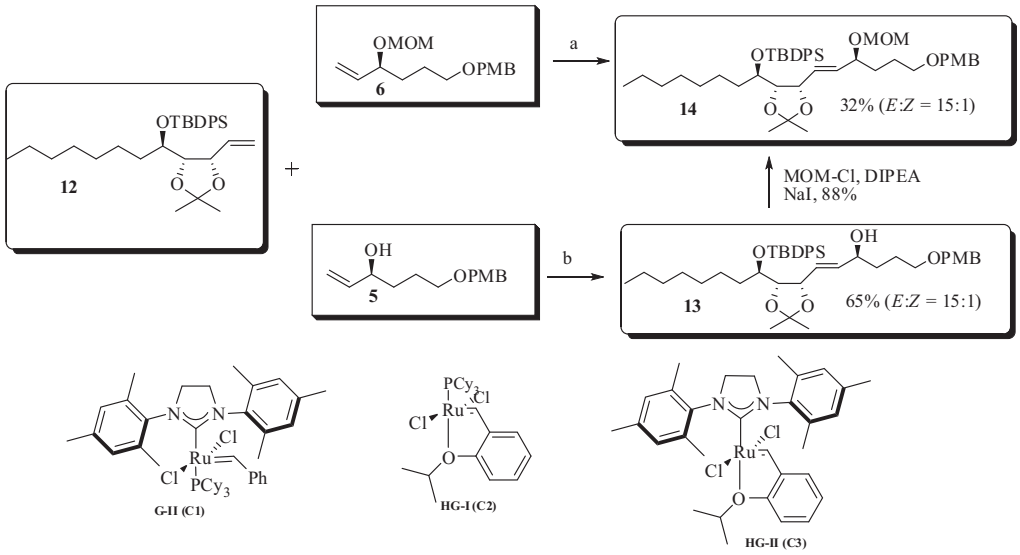
After successful construction of both the fragments, our next job is to couple them by cross metathesis reaction. One of the reacting partners in CM reaction was kept constant, and compound **12** was chosen for that purpose. Whereas for choosing the other partner we have performed a systematic optimization with compounds **5**



Scheme 3. Reagents and conditions: (a) (i) *S*-proline, PhNO, DMSO, rt, 3 h; (ii) $CuSO_4$, 0 °C, 6 h; (iii) Im, TBDPS-Cl, DMAP, DCM, rt, 6 h, 80% in three steps; (b) $(PhO)_2POCH_2CO_2Et$, NaH, THF, 0 °C, 88%; (c) OsO_4, NMO, THF:water (3:1), 12 h, 90%; (d) 2,2-DMP, CSA, DCM, rt, 88%; (e) DIBAL-H, THF, −78 °C, 76%; (f) $Ph_3P^+CH_3I^-$, LiHMDS, THF, 0 °C—rt, 80%.

and **6** with HG-II (Hoveyda–Grubbs Ru-based metathesis catalyst; Scheme 4). It was observed that both the compound **5** and **6** underwent CM reaction with compound **12** and furnished corresponding product **13** and **14** in 65% and 32% yield, respectively with commendable amount of stereocontrol (*E*:*Z*=15:1; Scheme 4). It was earlier demonstrated that compound containing a free 2° allylic alcohol moiety has a rate enhancement effect in RCM reaction.[21] The reason for that high activity of compound **5** is not very clear, but the possibility of rapid and reversible ligand exchange

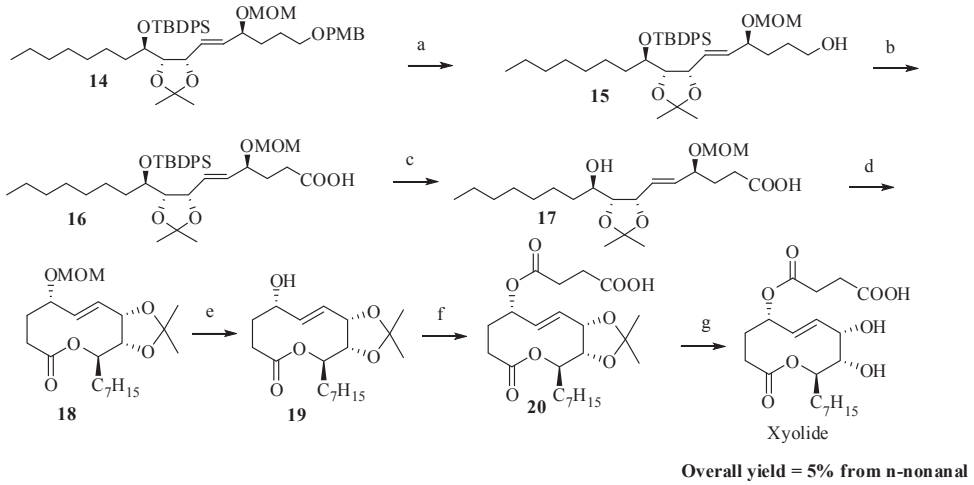
As the CM reaction went smoothly as anticipated the initial hurdle in the total synthesis is crossed. Next we have proceeded for our desired macrolactonization method to access the nonenolide core of xyolide. For that purpose PMB group was removed from compound **14** by treatment with DDQ to furnish alcohol **15** in 90% yield. Oxidation of the free hydroxyl group with DMP afforded the corresponding aldehyde, which on subsequent oxidation under Pinnick condition afforded compound **16** in 82% yield. Removal of the TBDPS group in compound **16** was accomplished by treatment



Scheme 4. Reagents and conditions: a) or b) HG-II (5 mol %), refluxing DCM, 24 h.

(alkoxy group replaces the Cl) and hydrogen bonding between hydroxyl group and one of the chloride ligands cannot be ruled out. The best results in the CM reaction (selectivity and reactivity; *E*:*Z*~15:1) were obtained with catalyst **C3** (Hoveyda–Grubbs second generation catalyst; HG-II).[22] With the catalyst **C1** (G-II),[23] the CM product was isolated in 30% yield with poor selectivity (*E*:*Z*~1:1). Whereas with catalyst **C2** (HG-I)[24] no product formation was detected, indicating that NHC type Ru-based metathesis catalyst is the ideal choice for best reactivity and selectivity.

with TBAF in THF as a solvent to the seco-acid **17** in 88% yield. The acid **17** on macrolactonization under Shiina condition[13] as shown in Scheme 5 afforded the corresponding nonenolide core of xyolide **18** in 68% yield. Selective deprotection of MOM group was achieved by treating the compound **18** with silica supported $KHSO_4$[25] to furnish compound **19** in 86% yield. Compound **19** was then treated with succinic anhydride, DCC, and DMAP to afford the half ester **20** in 90% yield. Finally deprotection of the acetonide functionality was accomplished by treating compound **20** with 2 N HCl in THF solvent



Scheme 5. Reagents and conditions: (a) DDQ, DCM:phosphate buffer (19:1), 1 h, rt, 90%; (b) (i) DMP, DCM, rt, 2 h, (ii) $NaClO_2$, NaH_2PO_4, ^tBuOH, 2-methyl-2-butene, H_2O, rt, 4 h, 82% in two-step; (c) TBAF, THF, 40 °C, 3 h, 88%; (d) MNBA (2-methyl-6-nitro benzoic anhydride), DIPEA (diisopropylethyl amine), DMAP, toluene, 60 °C, 24 h, 68%; (e) silica supported $KHSO_4$, DCM, rt, 4 h, 86%; (f) succinic anhydride, DCC, DMAP, 90%, rt, DCM, 24 h; (g) 2 N HCl, THF, rt, 12 h, 85%.

to furnish the target molecule xyolide in 85% yield (Scheme 5; overall yield=5% from *n*-nonanal).

3. Conclusions

In conclusion, an asymmetric total synthesis of naturally occurring nonenolide xyolide is presented in this article. The synthetic strategy delineated in this article employs a successful application of '*E*' selective CM reaction for the construction of required olefinic geometry in the target molecule followed by a macrolactonization reaction by Shiina protocol. In general the reported synthetic strategies for these type of small ring macrolides with an inbuilt unsaturation (*Z* or *E*), involve application of a successful late stage selective RCM (ring closing metathesis) reaction in all the cases. This altered sequence of chemical reaction, for example, CM followed by macrolactonization reported by us in this article could serve as an efficient strategy for the construction of small ring macrolide natural products in near future. We are currently exploring this strategy for the total synthesis of several structurally related naturally occurring small ring macrolides.

4. Experimental section

4.1. Materials and methods

All oxygen and/or moisture-sensitive reactions were carried out under N_2 atmosphere in glassware that had been flame-dried under a vacuum (~0.5 mmHg) and purged with N_2 prior to use. Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. CAL-B (immobilized on acrylic resin) was purchased from Sigma–Aldrich Co, USA. THF and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane (DCM), dimethylformamide (DMF), and dimethylsulfoxide (DMSO) were distilled from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, ethanolic anisaldehyde, and phosphomolybdic acid/heat as developing agents. Silicagel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on 400 & 200 MHz spectrometers at 25 °C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in δ. ^{13}C NMR spectra were recorded with a complete proton decoupling environment. The chemical shift value is listed as δ_H and δ_C for ^1H and ^{13}C, respectively. Mass spectrometric analysis was performed in the CRF, IIT-Kharagpur (TOF analyzer). Optical rotations were measured on a digital polarimeter. HPLC analysis was performed with CHIRALPAK AD-H & OJ-H (Daicel) column by using UV–vis detector.

*4.1.1. 4-(4-Methoxy-benzyloxy)-butan-1-ol (**1**).* Butane 1,4 diol (10 g, 111 mmol) was taken in 200 ml of dry THF. NaH (60% dispersion in mineral oil, 4.44 g, 111 mmol) was added to it portion wise at 0 °C. The reaction mixture was then stirred at 0 °C for 1 h. TBAI (5 mmol) was added to it followed by addition of 4-methoxybenzyl bromide. The reaction mixture was stirred further for 2 h at room temperature. Water was added carefully to the reaction mixture to quench any excess of NaH. The reaction mixture was then extracted with large volume of EtOAc, washed with brine. It was then dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography (EtOAc:hexane=1:3) to afford the compound **1** (20.51 g) in 88% yield.

R_f=0.3 (EtOAc:hexane=1:3). ^1H NMR of compound **1** (200 MHz, $CDCl_3$) δ: 7.26 (d, *J*=8.6 Hz, 2H), 6.88 (d, *J*=8.6 Hz, 2H), 4.45 (s, 2H), 3.80 (s, 3H), 3.64 (t, *J*=6.0 Hz, 2H), 3.50 (t, *J*=6.0 Hz, 2H), 1.74–1.64 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 159.2, 130.2, 129.4, 113.8, 72.6, 70.0, 62.4, 55.2, 29.9, 26.6.

*4.1.2. 4-(4-Methoxy-benzyloxy)-butyraldehyde (**2**).* Alcohol **1** (2.10 g, 10 mmol) was taken in dry DCM (40 ml) and cooled to 0 °C. Dess Martin Periodinane (DMP) (4.45 g, 10.5 mmol) was then added and the reaction mixture was warmed to room temperature over 1 h. The reaction mixture was then quenched with $Na_2S_2O_3$ and saturated $NaHCO_3$ solution successively and stirred for further 20 min. The resulting solution was then extracted with DCM. The organic extract was then dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography (EtOAc:hexane=1:5) to afford the compound **2** (1.87 g) in 90% yield.

R_f=0.3 (EtOAc:hexane=1:5). ^1H NMR of compound **2** (200 MHz, $CDCl_3$) δ: 9.78 (s, 1H), 7.26 (d, *J*=8.6 Hz, 2H), 6.90 (d, *J*=8.6 Hz, 2H), 4.43 (s, 2H), 3.81 (s, 3H), 3.49 (t, *J*=6.2 Hz, 2H), 2.58–2.50 (m, 2H), 1.98–1.91 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 202.4, 159.2, 130.3, 129.3, 113.8, 72.6, 68.8, 55.2, 40.9, 22.5.

*4.1.3. 6-(4-Methoxybenzyloxy)hex-1-en-3-ol (**3**).* Aldehyde **2** (5 g, 24 mmol) was taken in 40 ml of anhydrous THF. Solution of vinylmagnesium bromide (freshly prepared from vinyl bromide and Mg metal, 36 mmol) was added to it at −78 °C. The reaction mixture was kept at the same temperature for 1 h, after that time saturated NH_4Cl solution was added to it. The solution was then extracted with EtOAc, and the organic layer was washed with water and brine. The organic layer was dried ($MgSO_4$) and evaporated to afford the crude alcohol. Purification of the crude product by silica gel chromatography (EtOAc:hexane=1:3) afforded the racemic alcohol **3** (4.65 g) in 82% yield.

R_f=0.3 (EtOAc:hexane=1:3).

*4.1.4. (S)-6-(4-Methoxybenzyloxy)hex-1-en-3-yl acetate (**4**).* In a 50 ml round-bottom flask attached with a grease free high vacuum stopcock, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl) ruthenium (II) (DKR catalyst, 84 mg, 0.136 mmol) was taken. The flask was successively charged with alcohol **3** (0.80 g, 3.4 mmol) in 10 ml dry toluene, Na_2CO_3 (180 mg, 3.4 mmol), CAL-B (25 mg), and KO^{t}Bu (19 mg, 0.17 mmol) followed by isopropenyl acetate (0.58 ml, 5 mmol). The reaction mixture was then stirred at room temperature under argon atmosphere for almost 8 h. After completion of the reaction the mixture was filtered off and the solvent was evaporated to afford the crude acetate, which was subsequently purified by silica gel column chromatography (EtOAc:hexane=1:10) to afford the pure acetate **4** (83 mg) in 90% yield.

R_f=0.5 (EtOAc:hexane=1:10). $[\alpha]_D^{28}$ −6.8 (*c* 0.4, $CHCl_3$). ^1H NMR of compound **4** (200 MHz, $CDCl_3$) δ: 7.25 (d, *J*=8.6 Hz, 2H), 6.89 (d, *J*=8.6 Hz, 2H), 5.77 (ddd, *J*=6.2, 10.4, 17.4 Hz, 1H), 5.29–5.13 (m, 3H), 4.42 (s, 2H), 3.79 (s, 3H), 3.44 (t, *J*=5.6 Hz, 2H), 2.04 (s, 3H), 1.72–1.60 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.4, 159.2, 136.4, 130.6, 129.3, 116.8, 113.8, 74.6, 72.6, 69.5, 55.3, 30.9, 25.5, 21.3.

*4.1.5. (S)-6-(4-Methoxybenzyloxy)hex-1-en-3-ol (**5**).* To a solution of acetate compound **4** (834 mg, 3.0 mmol) in methanol was added K_2CO_3 (125 mg, 0.9 mmol) at room temperature and stirred for 1.5 h. After that time methanol was evaporated and water was added to the solution. The solution was then extracted with ethyl acetate. The organic extracts were then washed with brine and dried over $MgSO_4$. The organic solution was then concentrated in rotary evaporator and purified by column chromatography (EtOAc:hexane=1:10) to furnish the (*S*) alcohol **5** (651 mg) in 92% yield.

R_f=0.3 (EtOAc:hexane=1:3). $[\alpha]_D^{28}$ +9.9 (*c* 0.4, $CHCl_3$). ^1H NMR of compound **5** (200 MHz, $CDCl_3$) δ: 7.28 (d, *J*=8.4 Hz, 2H), 6.90 (d,

J=8.4 Hz, 2H), 5.88 (ddd, *J*=5.8, 10.4, 16.4 Hz, 1H), 5.27–5.07 (m, 2H), 4.46 (s, 2H), 4.16–4.10 (m, 1H), 3.81 (s, 3H), 3.53–3.47 (m, 2H), 1.71–1.61 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 159.2, 141.2, 130.3, 129.4, 114.4, 113.8, 72.6, 70.0, 55.3, 34.3, 25.8. HRMS (ESI) for $C_{14}H_{20}O_3Na$ $[M+Na]^+$, calculated: 259.1309; found: 259.1312.

*4.1.6. (S)-1-Methoxy-4-((4-(methoxymethoxy)hex-5-enyloxy) methyl)benzene (**6**).* To a solution of alcohol **5** (505 mg, 2.14 mmol) in DCM, diisopropyl ethyl amine (0.6 ml, 3.21 mmol) was added at 0 °C and stirred for 15 min at the same temperature. MOM-Cl (0.2 ml, 2.56 mmol) and tetra-*n*-butyl ammonium iodide (10 mg) was then added to the reaction mixture and stirred for additional 12 h at room temperature. Water was added to the reaction mixture and extracted with DCM. The organic extract was then washed with water and brine. The organic solvent was dried over $MgSO_4$, concentrated, and purified by silica gel column chromatography (EtOAc:hexane=1:10) to afford the desired product **6** (539 mg) in 90% yield.

R_f=0.4 (EtOAc:hexane=1:10). $[\alpha]_D^{28}$ +8.6 (*c* 0.3, $CHCl_3$). ^{1}H NMR of compound **6** (200 MHz, $CDCl_3$) δ: 7.28 (d, *J*=8.4 Hz, 2H), 6.88 (d, *J*=8.4 Hz, 2H), 5.73 (ddd, *J*=7.6, 9.8, 17.6 Hz, 1H), 5.26–5.17 (m, 2H), 4.72 (d, *J*=6.6 Hz, 1H), 4.55 (d, *J*=6.6 Hz, 1H), 4.46 (s, 2H), 4.07–4.00 (m, 1H), 3.81 (s, 3H), 3.52–3.43 (m, 2H), 3.38 (s, 3H), 1.73–1.61 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 159.2, 138.4, 130.8, 129.3, 117.3, 113.8, 93.8, 72.6, 69.9, 55.5, 55.3, 32.1, 25.8. HRMS (ESI) for $C_{16}H_{24}O_4Na$ $[M+Na]^+$, calculated: 303.1572; found: 303.1584.

*4.1.7. (R)-2-(tert-Butyldiphenylsilyloxy)nonanal (**7**).* *n*-Nonanal (256 mg, 2 mmol) was added at room temperature to a vial containing nitrosobenzene (107 mg, 1 mmol) and a catalytic amount of (*S*)-proline (11 mg, 10 mol %) in DMSO (4.0 ml). After 3 h reaction time, the temperature was lowered to 0 °C, followed by dilution with anhydrous MeOH (5.0 ml) and catalytic amount of $CuSO_4 \cdot 5H_2O$ (75 mg, 30 mol %). The reaction mixture was then stirred at this temperature for 6 h and then quenched by addition of aqueous NH_4Cl. The aqueous phase was extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, which was subsequently removed by filtration. The solvent was removed under reduced pressure.

R_f=0.5 (EtOAc:hexane=1:40).

The crude aldehyde (3.52 g, 22.3 mmol) was taken in anhydrous DCM (60 ml) and cooled to 0 °C. Imidazole (2.27 g, 33.45 mmol) and DMAP (100 mg, 0.81 mmol) were added to the reaction mixture followed by the addition of TBDPS-Cl (7 ml, 26.76 mmol). The reaction mixture was allowed to warm to room temperature for 6 h, after which water was added to it and the organic layer was washed with brine and dried over $MgSO_4$. Evaporation and purification by silica gel column chromatography (EtOAc:hexane=1:40) yielded the mono TBDPS-protected aldehyde **7** (633 mg) in 80% yield.

R_f=0.5 (EtOAc:hexane=1:40). $[\alpha]_D^{28}$ −5.1 (*c* 0.9, $CHCl_3$). ^{1}H NMR of compound **7** (200 MHz, $CDCl_3$) δ: 9.60 (d, *J*=1.4 Hz, 1H), 7.68–7.63 (m, 4H), 7.46–7.35 (m, 6H), 4.04 (t, *J*=5.8 Hz, 1H), 1.62–1.57 (m, 2H), 1.27–1.13 (m, 19H), 0.91–0.85 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 204.1, 136.0, 135.9, 133.3, 130.1, 127.9, 78.2, 33.0, 31.8, 29.6, 29.1, 27.1, 24.2, 22.7, 19.5, 14.2. HRMS (ESI) for $C_{25}H_{36}O_2SiNa$ $[M+Na]^+$, calculated: 419.2382; found: 419.2385.

*4.1.8. (R,Z)-Ethyl 4-(tert-butyldiphenylsilyloxy)undec-2-enoate (**8**).* To a solution of ethyl (diphenylphosphono) acetate (3.4 g, 10.7 mmol) in THF (40 ml) was added NaH (60%, 513 mg, 12.84 mmol) at 0 °C. After 15 min the aldehyde **7** (4.23 g, 10.7 mmol) in THF (10 ml) was added, and the resulting mixture was gradually warmed to the room temperature. After completion of the reaction as indicated by TLC analysis, water was added to the reaction mixture. Then it was extracted with ethyl acetate and washed with brine. The organic layer was dried over $MgSO_4$ and evaporated to afford the unsaturated ester (*Z*:*E*=14:1), which was further purified by flash chromatography (EtOAc:hexane=1:100) to afford pure **8** (4.2 g) in 88% yield.

R_f=0.3 (EtOAc:hexane=1:30). $[\alpha]_D^{28}$ +1.1 (*c* 1.1, $CHCl_3$). ^{1}H NMR of compound **8** (200 MHz, $CDCl_3$) δ: 7.69–7.62 (m, 4H), 7.43–7.27 (m, 6H), 6.17 (dd, *J*=8.2, 11.6 Hz, 1H), 5.48 (d, *J*=11.6 Hz, 1H), 5.40–5.31 (m, 1H), 4.00 (q, *J*=7.0 Hz, 2H), 1.69–1.52 (m, 2H), 1.31–1.19 (m, 11H), 1.18–1.09 (m, 11H), 0.92–0.86 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 165.7, 152.5, 136.0, 134.4, 134.3, 129.6, 127.6, 127.5, 117.9, 70.1, 60.0, 37.6, 31.9, 29.7, 29.3, 27.2, 24.8, 22.8, 19.5, 14.2. HRMS (ESI) for $C_{29}H_{42}O_3Si$ $[M+H]^+$, calculated: 467.2981; found: 467.3016.

*4.1.9. (R,E)-Ethyl 4-(tert-butyldiphenylsilyloxy)undec-2-enoate (**8**).* ^{1}H NMR of compound **8** (200 MHz, $CDCl_3$) δ: 7.71–7.61 (m, 4H), 7.45–7.36 (m, 6H), 6.88 (dd, *J*=5.2, 15.6 Hz, 1H), 5.91 (d, *J*=15.2 Hz, 1H), 4.37–4.32 (m, 1H), 4.18 (q, *J*=7.0 Hz, 2H), 1.43–1.40 (m, 2H), 1.34–1.14 (m, 11H), 1.10–1.00 (m, 11H), 0.92–0.86 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 166.8, 150.4, 136.0, 134.2, 133.8, 129.9, 127.8, 120.3, 72.7, 60.4, 37.0, 31.9, 29.5, 29.2, 27.2, 24.1, 22.8, 19.6, 14.4, 14.2. $[\alpha]_D^{28}$ +4.1 (*c* 1.1, $CHCl_3$).

*4.1.10. (2R,3S,4R)-Ethyl 4-(tert-butyldiphenylsilyloxy)-2,3-dihydroxyundecanoate (**9**).* The TBDPS-protected ester **8** (8.31 g, 17.84 mmol) was taken in THF:H_2O (3:1), OsO_4 (0.05 M, 17.9 ml, 0.89 mmol), and NMO (3.13 g, 26.76 mmol) was added at room temperature and stirred for 12 h, after which saturated solution of $NaHSO_3$ (2.7 g, 26.76 mmol) was added and the solution was further stirred for 2 h. The organic layer was extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. Then it was evaporated to dryness to afford the crude diol, which was further purified by flash chromatography (EtOAc:hexane=1:5) to afford pure **9** (8.1 g) in 90% yield.

R_f=0.4 (EtOAc:hexane=1:5). $[\alpha]_D^{28}$ +3.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR of compound **9** (200 MHz, $CDCl_3$) δ: 7.72–7.69 (m, 4H), 7.45–7.36 (m, 6H), 4.27–4.14 (m, 3H), 3.98–3.92 (m, 1H), 3.66–3.62 (m, 1H), 1.72–1.56 (m, 2H), 1.29–1.22 (m, 7H), 1.21–0.97 (m, 15H), 0.87–0.80 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 173.6, 136.1, 136.0, 133.9, 130.1, 129.9, 127.9, 127.7, 74.0, 73.5, 72.2, 61.8, 33.4, 31.8, 29.3, 29.1, 27.2, 24.9, 22.7, 19.6, 14.3, 14.2. HRMS (ESI) for $C_{29}H_{44}O_5SiNa$ $[M+Na]^+$, calculated: 523.2855; found: 523.2857.

*4.1.11. (4R,5S)-Ethyl 5-((R)-1-(tert-butyldiphenylsilyloxy)octyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (**10**).* Compound **9** (1.94 g, 4 mmol) was taken in 20 ml of dry DCM. 2,2-Dimethoxypropane (DMP, 1.5 ml, 12 mmol) was added to it followed by addition of catalytic amount of CSA (0.45 mmol, 122 mg). The reaction mixture was then stirred at room temperature for overnight. Water was added to the reaction mixture. Then it was extracted with DCM and washed with brine. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The product was purified by silica gel column chromatography (EtOAc:hexane=1:20) to afford the compound **10** (1.9 g) in 88% yield.

R_f=0.6 (EtOAc:hexane=1:10). $[\alpha]_D^{28}$ +1.3 (*c* 1.4, $CHCl_3$). ^{1}H NMR of compound **10** (200 MHz, $CDCl_3$) δ: 7.74–7.67 (m, 4H), 7.41–7.26 (m, 6H), 4.42–4.39 (m, 1H), 4.31–4.20 (m, 1H), 3.99–3.87 (m, 2H), 3.76–3.67 (m, 1H), 1.40 (s, 6H), 1.20–1.12 (m, 12H), 1.11–1.00 (m, 12H), 0.91–0.84 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 170.3, 136.3, 134.7, 134.6, 129.4, 129.2, 127.4, 127.1, 110.7, 81.3, 76.1, 72.5, 61.0, 34.1, 31.9, 29.8, 29.3, 27.3, 26.5, 25.5, 25.1, 22.8, 19.9, 14.2, 14.0. HRMS (ESI) for $C_{32}H_{48}O_5SiNa$ $[M+Na]^+$, calculated: 563.3168; found: 563.3172.

*4.1.12. (4R,5S)-5-(R)-1-((tert-Butyldiphenylsilyloxy)octyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**11**).* The compound **10** (1.51 g, 2.8 mmol) was taken in dry DCM (10 ml) and cooled to

−78 °C. Solution of DIBAL-H (1 M in DCM, 2.8 ml) was added to it for a period of 30 min. The reaction was stirred for further 2 h at the same temperature and then warmed to −20 °C and quenched with dry methanol and stirred for further 1.5 h. Then it was extracted with ethyl acetate, washed with brine, and dried over $MgSO_4$. The organic extract was evaporated to dryness to afford the crude product, which was then purified by silica gel column chromatography (EtOAc:hexane=1:20) to afford the compound **11** (1.05 g) in 76% yield.

R_f=0.5 (EtOAc:hexane=1:15). ^{1}H NMR of compound **11** (200 MHz, $CDCl_3$) δ: 9.66 (d, J=2.8 Hz, 1H), 7.80–7.67 (m, 4H), 7.40–7.37 (m, 6H), 4.44–4.38 (m, 1H), 4.33–4.27 (m, 1H), 3.83 (q, J=5.6 Hz, 1H), 1.33–1.07 (m, 8H), 1.06–0.87 (m, 19H), 0.86–0.80 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 201.1, 136.2, 134.4, 134.1, 129.6, 127.6, 127.5, 110.7, 81.2, 81.0, 71.5, 33.3, 31.8, 29.3, 29.1, 27.1, 25.6, 25.0, 22.7, 19.6, 14.2.

*4.1.13. tert-Butyl (R)-1-((4S,5S)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)octyloxy)diphenylsilane) (**12**).* To a suspension of methyltriphenylphosphonium iodide (646 mg, 1.6 mmol) in dry THF (2 ml) was added LiHMDS (1.0 M solution in THF, 1.6 ml) at 0 °C. The yellow mixture was then stirred at 0 °C for 15 min. A solution of the aldehyde **11** (397 mg, 0.8 mmol) in 1 ml of THF was added to the reaction mixture. The yellow suspension was stirred at room temperature for further 1 h. After completion of the reaction, as indicated by TLC analysis, the reaction was quenched with water and the layers were separated. It was then extracted with ether and the organic layer was washed with brine. It was then dried with $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude residue was purified by flash column chromatography (EtOAc:hexane=1:30) to afford the compound **12** (316 mg) in 80% yield.

R_f=0.5 (EtOAc:hexane=1:30). $[\alpha]_D^{28}$ +1.7 (*c* 1.0, $CHCl_3$). ^{1}H NMR of compound **12** (200 MHz, $CDCl_3$) δ: 7.79–7.76 (m, 4H), 7.42–7.36 (m, 6H), 5.70–5.52 (m, 1H), 5.21–5.07 (m, 2H), 4.39–4.32 (m, 1H), 4.21–4.14 (m, 1H), 3.81–3.71 (m, 1H), 1.32–1.11 (m, 14H), 1.10–0.94 (m, 10H), 0.91–0.88 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 136.4, 134.8, 129.4, 129.2, 127.8, 127.3, 127.1, 118.7, 108.5, 81.0, 79.3, 72.2, 33.2, 31.9, 29.6, 29.2, 28.1, 27.4, 25.4, 25.0, 22.8, 19.8, 14.2. HRMS (ESI) for $C_{31}H_{46}O_3SiNa$ $[M+Na]^+$, calculated: 517.3113; found: 517.3100.

4.2. General procedure for cross metathesis

Olefin **12** (492 mg, 1 mmol) was taken in a flame-dried round-bottom flask and the 2° allylic alcohol (**5**/**6**, 2 mmol) in DCM (10 ml) was added to it. Hoveyda–Grubbs catalyst (HG-II; 31 mg, 0.05 mmol) was then added to the reaction solution under inert atmosphere. The light green solution was then refluxed for 24 h under argon atmosphere and then it was concentrated in vacuo to afford dark brown oil. Purification of this residue on silica gel by flash chromatography (EtOAc:hexane=1:20) afforded the compound **13**/**14** in 65% and 32%, respectively as a yellow oil.

*4.2.1. (S,E)-1-((4S,5S)-5-((R)-1-(tert-Butyldiphenylsilyloxy)octyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-6-(4-methoxybenzyloxy)hex-1-en-3-ol (**13**).* ^{1}H NMR of compound **13** (200 MHz, $CDCl_3$) δ: 7.76–7.73 (m, 4H), 7.40–7.30 (m, 8H), 6.92–6.88 (m, 2H), 5.41–5.35 (m, 2H), 4.34–4.28 (m, 3H), 4.17–4.09 (m, 1H), 3.88–3.85 (m, 1H), 3.81 (s, 3H), 3.65–3.63 (m, 1H), 3.42–3.35 (m, 2H), 1.70–1.61 (m, 4H), 1.54–1.36 (m, 12H), 1.34–1.09 (m, 15H), 0.92–0.88 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.2, 136.1, 136.1, 134.5, 134.3, 130.6, 129.2, 129.0, 127.2, 126.9, 113.7, 108.4, 80.8, 78.1, 75.5, 72.1, 69.7, 55.4, 33.1, 32.1, 31.6, 29.8, 29.5, 29.1, 28.0, 27.2, 25.7, 25.3, 24.9, 22.6, 19.5, 14.1. R_f=0.3 (EtOAc:hexane=1:10). $[\alpha]_D^{28}$ −3.9 (*c* 0.4, $CHCl_3$). HRMS (ESI) for $C_{43}H_{62}O_6SiNa$ $[M+Na]^+$, calculated: 725.4213; found: 725.4210.

*4.2.2. tert-Butyl((R)-1-((4S,5S)-5-((S,E)-6-(4-methoxybenzyloxy)-3-(methoxymethoxy)hex-1-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)octyloxy)diphenylsilane (**14**).* ^{1}H NMR of compound **14** (400 MHz, $CDCl_3$) δ: 7.73–7.71 (m, 4H), 7.40–7.33 (m, 6H), 7.31–7.24 (m, 2H), 6.89–6.87 (m, 2H), 5.41 (dd, J=6.2, 15.6 Hz, 1H), 5.32 (dd, J=8.0, 15.6 Hz, 1H), 4.49 (d, J=6.8 Hz, 1H), 4.44 (s, 2H), 4.38 (d, J=7.2 Hz, 1H), 4.32 (t, J=6.8 Hz, 1H), 4.11 (t, J=7.0 Hz, 1H), 3.88–3.85 (m, 1H), 3.81 (s, 3H), 3.65–3.63 (m, 1H), 3.40–3.37 (m, 2H), 3.31 (s, 3H), 1.66–1.60 (m, 4H), 1.54–1.36 (m, 12H), 1.34–1.19 (m, 6H), 1.21–1.09 (m, 9H), 0.90–0.86 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.1, 136.2, 136.1, 134.5, 134.3, 130.6, 129.2, 129.0, 127.2, 126.9, 113.7, 108.3, 93.7, 80.8, 78.0, 75.5, 72.1, 69.7, 55.4, 55.2, 33.1, 32.1, 31.7, 29.8, 29.7, 29.1, 28.0, 27.2, 25.7, 25.3, 24.8, 22.6, 19.6, 14.1. R_f=0.5 (EtOAc:hexane=1:10). $[\alpha]_D^{28}$ −1.9 (*c* 0.2, $CHCl_3$). HRMS (ESI) for $C_{45}H_{66}O_7SiNa$ $[M+Na]^+$, calculated: 769.4474; found: 769.4481.

*4.2.3. (S,E)-6-((4S,5S)-5-((R)-1-(tert-Butyldiphenylsilyloxy)octyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(methoxymethoxy)hex-5-en-1-ol (**15**).* Compound **14** (292 mg, 0.4 mmol) was taken in 3 ml of DCM/H_2O (19:1). DDQ (90 mg, 0.4 mmol) was added to it in one portion. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then filtered off, and the filtrate was washed with saturated $NaHCO_3$ solution, water, and brine. The organic layer was dried ($MgSO_4$) and evaporated in vacuo to afford the crude product. Purification of the crude residue by silica gel column chromatography (EtOAc:hexane=1:3) afforded the desired product **15** (225 mg) in 90% yield as an oil.

R_f=0.5 (EtOAc:hexane=1:5). $[\alpha]_D^{28}$ −1.3 (*c* 0.3, $CHCl_3$). ^{1}H NMR of compound **15** (200 MHz, $CDCl_3$) δ: 7.77–7.73 (m, 4H), 7.45–7.30 (m, 6H), 5.49–5.30 (m, 2H), 4.53 (d, J=6.6 Hz, 1H), 4.46–4.32 (m, 2H), 4.18–4.11 (m, 1H), 3.95–3.91 (m, 1H), 3.67–3.62 (m, 3H), 3.35 (s, 3H), 1.58–1.49 (m, 4H), 1.33–1.26 (m, 13H), 1.22–0.92 (m, 15H), 0.88–0.87 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 136.1, 134.4, 133.9, 129.2, 129.0, 127.1, 126.9, 108.3, 93.7, 80.7, 77.9, 75.4, 72.1, 62.6, 55.5, 33.1, 31.9, 31.6, 29.6, 29.0, 28.4, 28.0, 27.1, 25.3, 24.8, 22.5, 19.6, 14.0. HRMS (ESI) for $C_{37}H_{58}O_6SiNa$ $[M+Na]^+$, calculated: 649.3900; found: 649.3912.

*4.2.4. (S,E)-6-((4S,5S)-5-((R)-1-(tert-Butyldiphenylsilyloxy)octyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(methoxymethoxy)hex-5-enoic acid (**16**).* Alcohol **15** (187 mg, 0.3 mmol), was taken in dry DCM (10 ml) and cooled to 0 °C. Dess Martin Periodinane (DMP) (259 mg, 0.4 mmol) was then added and warmed to room temperature over 2 h. The reaction mixture was quenched with $Na_2S_2O_3$ and saturated $NaHCO_3$ solution successively and stirred for further 20 min. The organic solution was then dried with $MgSO_4$, filtered, and the solvent was removed in vacuo to afford the crude aldehyde, which was used subsequently for the next step.

To a solution of the crude aldehyde (180 mg, 0.3 mmol) in *tert*-butanol (8 ml), 2-methyl-2-butene (4 ml) was added dropwise, then a solution of sodium phosphate monobasic (153 mg, 1.28 mmol) and sodium chlorite (232 mg, 2.56 mmol) in water (4 ml) was added. The solution was stirred for 4 h at room temperature, then ethyl acetate and water was added to the reaction mixture. The aqueous layer was extracted twice with EtOAc. The combined organic layers were washed with water and brine and dried with $MgSO_4$. Concentrated and purified by column chromatography (EtOAc:hexane=1:2) to afford the carboxylic acid **16** (157 mg) in 82% yield.

R_f=0.3 (EtOAc:hexane=1:3). $[\alpha]_D^{28}$ +0.9 (*c* 0.2, $CHCl_3$). ^{1}H NMR of compound **16** (200 MHz, $CDCl_3$) δ: 7.77–7.73 (m, 4H), 7.44–7.30 (m, 6H), 5.43–5.40 (m, 2H), 4.49 (d, J=7.0 Hz, 1H),

4.41–4.32 (m, 2H), 4.18–4.11 (m, 1H), 3.97–3.94 (m, 1H), 3.67–3.62 (m, 1H), 3.34 (s, 3H), 2.44–2.36 (m, 2H), 1.78–1.70 (m, 2H), 1.35–1.30 (m, 9H), 1.29–1.21 (m, 9H), 1.20–1.00 (m, 9H), 0.93–0.86 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 178.2, 136.4, 134.7, 133.5, 129.9, 129.5, 129.3, 127.4, 127.1, 108.6, 94.0, 81.0, 78.0, 74.7, 72.3, 55.8, 33.4, 31.9, 30.3, 29.9, 29.3, 28.2, 27.4, 25.5, 25.0, 22.8, 19.8, 14.3. HRMS (ESI) for $C_{37}H_{56}O_7SiNa$ $[M+Na]^+$, calculated: 663.3692; found: 663.3677.

*4.2.5. (S,E)-6-((4S,5R)-5-((R)-1-Hydroxyoctyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(methoxymethoxy)hex-5-enoic acid (**17**).* Compound **16** (128 mg, 0.2 mmol) was taken in dry THF (2 ml). TBAF (1 M in THF, 0.4 ml, 0.4 mmol) was added to the solution, and the reaction mixture was then stirred for 3 h at 40 °C. THF was then evaporated, and water (2 ml) was added to it, the reaction mixture was extracted with EtOAc (50 ml), the organic layer was washed with $NaHCO_3$ and brine, and dried (Na_2SO_4). It was purified by flash chromatography (EtOAc:hexane=1:1) to afford compound **17** (70 mg) in 88% yield.

R_f=0.1 (EtOAc:hexane=1:2). $[\alpha]_D^{28}$ +9.9 (*c* 0.2, $CHCl_3$). ^{1}H NMR of compound **17** (200 MHz, $CDCl_3$) δ: 5.43–5.33 (m, 2H), 4.50–4.45 (m, 1H), 4.43–4.29 (m, 2H), 4.12–4.09 (m, 1H), 3.95–3.92 (m, 1H), 3.64–3.56 (m, 1H), 3.27 (s, 3H), 2.38–2.34 (m, 2H), 1.73–1.70 (m, 2H), 1.38–1.26 (m, 9H), 1.25–1.15 (m, 9H), 0.87–0.84 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 178.2, 108.6, 94.0, 81.0, 78.0, 74.8, 72.3, 55.8, 33.5, 31.9, 30.3, 29.9, 29.3, 28.2, 27.5, 25.5, 25.0, 22.8, 19.8, 14.3. HRMS (ESI) for $C_{21}H_{38}O_7Na$ $[M+Na]^+$, calculated: 425.2515; found: 425.2518.

*4.2.6. (3aR,4R,9S,11aS,E)-4-Heptyl-9-(methoxymethoxy)-2,2-dimethyl-7,8,9,11a-tetrahydro-3aH-[1,3]dioxolo[4,5-c]oxecin-6(4H)-one (**18**).* To a solution of MBNA (46 mg, 0.13 mmol), DIPEA (0.181 ml, 1.05 mmol), and DMAP (15 mg, 0.12 mmol) in toluene (35 ml) at room temperature was added a solution of seco-acid **17** (41 mg, 0.1 mmol) in toluene (15 ml). After that the reaction mixture was stirred for 24 h at 60 °C, then cooled to room temperature and quenched by adding saturated aqueous $NaHCO_3$ solution. The organic solution was then successively washed with water, brine, and dried over $MgSO_4$. The organic solvent was evaporated to furnish the crude product, which was purified by silica gel column chromatography (EtOAc:hexane=1:20) to afford the lactone **18** (26 mg) in 68% yield.

R_f=0.3 (EtOAc:hexane=1:10). $[\alpha]_D^{28}$ +11.9 (*c* 0.3, $CHCl_3$). ^{1}H NMR of compound **18** (200 MHz, $CDCl_3$) δ: 5.84 (dd, *J*=3.8, 15.4 Hz, 1H), 5.38–5.24 (m, 2H), 4.75 (d, *J*=6.6 Hz, 1H), 4.56 (d, *J*=6.6 Hz, 1H), 4.43–4.36 (m, 1H), 4.17–4.08 (m, 2H), 3.38 (s, 3H), 2.45–2.23 (m, 4H), 1.71–1.60 (m, 2H), 1.44 (s, 3H), 1.38 (s, 3H), 1.32–1.10 (m, 10H), 0.90–0.87 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 175.0, 133.9, 130.0, 108.2, 94.2, 79.0, 78.2, 77.8, 68.9, 55.6, 32.9, 31.9, 31.4, 29.9, 29.4, 29.3, 28.9, 26.1, 25.5, 22.8, 14.2. HRMS (ESI) for $C_{21}H_{36}O_6Na$ $[M+Na]^+$, calculated: 407.2409; found: 407.2412.

*4.2.7. (3aR,4R,9S,11aS,E)-4-Heptyl-9-hydroxy-2,2-dimethyl-7,8,9,11a-tetrahydro-3aH-[1,3]dioxolo[4,5-c]oxecin-6(4H)-one (**19**).* To a solution of compound **18** (69 mg, 0.18 mmol) in dry DCM (10 ml) was added activated $KHSO_4{\cdot}SiO_2$ (0.68 g, 4.3 mmol). The reaction mixture was stirred for 4 h at room temperature then filtered through a plug of cotton wool and washed with ethyl acetate until the filtrate dripped clear. The filtrate was concentrated in vacuo to give a black residue. Purification of the residue by flash column chromatography using (EtOAc:hexane=1:10) afforded alcohol **19** (52 mg, 86%) as a yellow oil.

R_f=0.4 (EtOAc:hexane=1:5). $[\alpha]_D^{28}$ +39.9 (*c* 0.2, $CHCl_3$). ^{1}H NMR of compound **19** (200 MHz, $CDCl_3$) δ: 5.82 (dd, *J*=3.2, 15.8 Hz, 1H), 5.66 (dd, *J*=1.6, 8.4 Hz, 1H), 4.96–4.90 (m, 1H), 4.70–4.67 (m, 1H), 4.21–3.98 (m, 2H), 2.37–2.31 (m, 2H), 2.09–2.01 (m, 2H), 1.85–1.74 (m, 2H), 1.55 (s, 3H), 1.38 (s, 3H), 1.34–1.21 (m, 10H), 0.88–0.84 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 175.0, 128.1, 126.6, 109.3, 78.5, 75.7, 70.1, 33.6, 31.9, 31.8, 31.2, 29.4, 29.2, 28.4, 26.2, 24.5, 22.6, 14.0. HRMS (ESI) for $C_{19}H_{32}O_5Na$ $[M+Na]^+$, calculated: 363.2145; found: 363.2148.

*4.2.8. 4-((3aR,4R,9S,11aS,E)-4-Heptyl-2,2-dimethyl-6-oxo-4,6,7,8,9,11a-hexahydro-3aH-[1,3]dioxolo[4,5-c]oxecin-9-yloxy)-4-oxobutanoic acid (**20**).* Succinic anhydride (22 mg, 0.22 mmol) was taken in dry DCM (2 ml). DCC (61 mg, 0.3 mmol), DMAP (5 mg), and alcohol **19** (50 mg, 0.15 mmol) were sequentially added to the reaction mixture. The reaction mixture was kept at room temperature for 24 h. DCM was evaporated and the crude ester was purified by flash chromatography (EtOAc:hexane=1:10) to afford the ester **20** (60 mg) in 90% yield.

R_f=0.4 (EtOAc:hexane=1:10). $[\alpha]_D^{28}$ +31.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR of compound **20** (400 MHz, $CDCl_3$) δ: 5.91 (dd, *J*=3.2, 15.2 Hz, 1H), 5.63 (dd, *J*=2.4, 8.8 Hz, 1H), 5.29–5.18 (m, 1H), 4.96–4.88 (m, 1H), 4.72–4.67 (m, 1H), 3.98 (dd, *J*=4.4, 9.6 Hz, 1H), 2.77–2.55 (m, 4H), 2.40–2.28 (m, 2H), 2.19–1.99 (m, 4H), 1.54 (s, 3H), 1.36 (s, 3H), 1.34–1.18 (m, 10H), 0.88–0.84 (m, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 177.3, 174.1, 171.3, 128.2, 123.7, 109.4, 78.5, 76.9, 75.5, 71.0, 31.9, 31.7, 30.9, 30.5, 29.3, 29.1, 28.9, 28.5, 28.4, 26.1, 24.4, 22.6, 14.0. HRMS (ESI) for $C_{23}H_{36}O_8Na$ $[M+Na]^+$, calculated: 463.2290; found: 463.2284.

4.2.9. 4-((5S,8S,9S,10R,E)-10-Heptyl-8,9-dihydroxy-2-oxo-3,4,5,8,9,10-hexahydro-2H-oxecin-5-yloxy)-4-oxobutanoic acid (xyolide). To a solution of compound **20** (26 mg, 0.06 mmol) in THF (5 ml), HCl (1 ml, 2 M) was added at room temperature and stirred for 12 h. Water was added to the reaction mixture and it was extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$ and brine. It was then dried over $MgSO_4$, concentrated in a rotary evaporator, and purified by silica gel column chromatography (EtOAc:hexane=1:1) to afford the target molecule xyolide (21 mg) in 85% yield.

R_f=0.3 (EtOAc:hexane=2:1). $[\alpha]_D^{28}$ +10.1 (*c* 0.8, $CHCl_3$). ^{1}H NMR of Xyolide (400 MHz, $CDCl_3$) δ: 5.86 (dd, *J*=1.8, 15.4 Hz, 1H), 5.50 (ddd, *J*=1.4, 9.6, 15.4 Hz, 1H), 5.18–5.10 (m, 1H), 4.99 (td, *J*=1.8, 9.6 Hz, 1H), 4.52–4.49 (m, 1H), 3.60 (dd, *J*=1.8, 9.6 Hz, 1H), 2.67 (t, *J*=6.2 Hz, 2H), 2.62 (t, *J*=5.8 Hz, 2H), 2.40–2.31 (m, 1H), 2.12–1.98 (m, 3H), 1.91–1.82 (m, 1H), 1.57–1.48 (m, 1H), 1.37–1.17 (m, 10H), 0.88 (t, *J*=6.8 Hz, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ: 176.5, 174.5, 171.6, 132.6, 123.5, 76.4, 73.5, 72.5, 70.8, 31.7, 31.5, 31.2, 29.6, 29.4, 29.3, 29.1, 28.8, 24.5, 22.6, 14.0. HRMS (ESI) for $C_{20}H_{32}O_8Na$ $[M+Na]^+$, calculated: 423.1982; found: 423.1978.

Acknowledgements

Financial support from CSIR-India is gratefully acknowledged (Grant: 02(0020)/11/EMR-II). We are also thankful to DST-India (IRPHA) for NMR instrument. One of the authors R.K.R. is thankful to CSIR-India for providing research fellowship.

Supplementary data

Copies of ^{1}H, ^{13}C NMR spectra of all compounds, and HPLC chromatogram of racemic and enantiopure **3** and **7** is provided. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.02.072.

References and notes

1. Strobel, G. A.; Knighton, B.; Kluck, K.; Ren, Y.; Livinghouse, T.; Griffin, M.; Spakowicz, D.; Sears, J. *Microbiology* **2008**, *154*, 3319–3328.

2. Smith, S. A.; Tank, D. C.; Boulanger, L. A.; Bascom-Slack, C. A.; Eisenman, K.; Kingery, D.; Babbs, B.; Fenn, K.; Greene, J. S.; Hann, B. D.; Keehner, J.; Kelley-Swift, E. G.; Kembaiyan, V. S.; Lee, J.; Li, P.; Light, D. Y.; Lin, E. H.; Ma, C.; Moore, E.; Schorn, M. A.; Vekhter, D.; Nunez, P. V.; Strobel, G. A.; Donoghue, M. J.; Strobel, S. A. *PLoS One* **2008**, *3*, e3052.
3. Baraban, E. G.; Morin, J. B.; Phillips, G. M.; Phillips, A. J.; Strobel, S. A.; Handelsman, J. *Tetrahedron Lett.* **2013**, *54*, 4058–4060.
4. (a) Lu, S.; Sun, P.; Li, T.; Kurtan, T.; Mandi, A.; Antus, S.; Krohn, K.; Draeger, S.; Schulz, B.; Yi, Y.; Li, L.; Zhang, W. *J. Org. Chem.* **2011**, *76*, 9699–9710; (b) Lu, S.; Kurtan, T.; Genjin, Y.; Sun, P.; Mandi, A.; Krohn, K.; Draeger, S.; Schulz, B.; Yi, Y.; Li, L.; Zhang, W. *Eur. J. Org. Chem.* **2011**, *28*, 5452–5469.
5. (a) Rivero-Cruz, J. F.; Garcia-Aguirre, G.; Cerda-Garcia-Rojas, C. M.; Mata, R. *Tetrahedron* **2000**, *56*, 5337–5344; (b) Rivero-Cruz, J. F.; Garcia-Aguirre, G.; Cerda-Garcia-Rojas, C. M.; Mata, R. *J. Nat. Prod.* **2003**, *66*, 511–514.
6. Evidente, A.; Capasso, R.; Andolfi, A.; Vurro, M.; Chiara Zonno, M. *Nat. Toxins* **1999**, *6*, 183–190.
7. Evidente, A.; Lanzetta, R.; Capasso, R.; Vurro, M.; Bottalico, A. *Phytochemistry* **1993**, *34*, 999–1003.
8. Bodo, B.; Molho, L.; Davoust, D.; Molho, D. *Phytochemistry* **1983**, *22*, 447–451.
9. Hiep, N. T.; Choi, Y.-h.; Kim, N.; Hong, S. S.; Hong, S. B.; Hwang, B. Y.; Lee, H. J.; Jang, D. S.; Lee, D. *J. Nat. Prod.* **2012**, *75*, 784–788.
10. (a) Reddy, B. V. S.; Reddy, P. S.; Reddy, B. P.; Yadav, J. S.; Ghamdi, A. A. K. A. *Tetrahedron Lett.* **2013**, *54*, 5758–5760; (b) Mohapatra, D. K.; Reddy, D. P.; Karhale, D. S.; Yadav, J. S. *Synlett* **2013**, 2679–2682.
11. (a) Rej, R. K.; Nanda, S. *Eur. J. Org. Chem.* **2014**, 860–871; (b) Jana, N.; Das, D.; Nanda, S. *Tetrahedron* **2013**, *69*, 2900–2908; (c) Jana, N.; Nanda, S. *Tetrahedron: Asymmetry* **2012**, *23*, 802–808; (d) Jana, N.; Nanda, S. *Eur. J. Org. Chem.* **2012**, 4313–4320; (e) Das, T.; Mahapatra, T.; Nanda, S. *Tetrahedron Lett.* **2012**, *53*, 1186–1189; (f) Das, T.; Nanda, S. *Tetrahedron Lett.* **2012**, *53*, 256–258; (g) Das, T.; Bhuniya, R.; Nanda, S. *Tetrahedron: Asymmetry* **2010**, *21*, 2206–2211; (h) Das, T.; Jana, N.; Nanda, S. *Tetrahedron Lett.* **2010**, *51*, 2644–2647; (i) Jana, N.; Mahapatra, T.; Nanda, S. *Tetrahedron: Asymmetry* **2009**, *20*, 2622–2628.
12. (a) *Metathesis in Natural Product Synthesis*; Arseniyadis, J. S., Meyer, C., Eds.; Wiley-VCH: Weinheim, Germany, 2010; pp 287–310; (b) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.
13. (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993; (b) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. *J. Org. Chem.* **2004**, *69*, 1822–1830.
14. Pellissier, H. *Chirality from Dynamic Kinetic Resolution*; RSC: Cambridge, UK, 2011; pp 191–242.
15. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
16. (a) Choi, J. H.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M. J.; Park, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2373–2376; (b) Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M. J.; Park, J. *J. Org. Chem.* **2004**, *69*, 1972–1977; (c) Kim, M. J.; Chung, Y. I.; Choi, Y. K.; Lee, H. K.; Kim, D.; Park, J. *J. Am. Chem. Soc.* **2003**, *125*, 11494–11495.
17. The enantioselectivity was determined by Chiral-HPLC (CHIRALPAK IA from Daicel, 254 nm) by deprotecting the acetate group and converting the free alcohol group to its benzoate ester.
18. (a) Kumar, P.; Dwivedi, N. *Acc. Chem. Res.* **2013**, *46*, 289–299; (b) Cordova, A.; Sunden, H.; Bogevig, A.; Johansson, M.; Himo, F. *Chem.—Eur. J.* **2004**, *10*, 3673–3684.
19. Ando, K. *J. Org. Chem.* **1997**, *62*, 1934–1939.
20. Cha, J. K.; Christ, W. C.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247–2255.
21. (a) Hoye, T. R.; Zhao, H. *Org. Lett.* **1999**, *1*, 1123–1125; (b) Srihari, P.; Kumaraswamy, B.; Somaiah, R.; Yadav, J. S. *Synthesis* **2010**, *6*, 1039–1045; (c) Mohapatra, D. K.; Dash, U.; Naidu, P. R.; Yadav, J. S. *Synlett* **2009**, 2129–2132.
22. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
23. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
24. Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1999**, *121*, 791–799.
25. Rathwell, D. C. K.; Yang, S. H.; Tsang, K. Y.; Brimble, M. A. *Angew. Chem., Int. Ed.* **2009**, *48*, 7996–8000.