J. Chem. Sci. Vol. 126, No. 6, November 2014, pp. 1841–1847.

(S)-Garner aldehyde derived Baylis-Hillman adduct: A potential substrate for the synthesis of D-*lyxo* phytosphinosine analogue

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MS received 3 February 2014; revised 19 April 2014; accepted 25 April 2014

Abstract. A short, facile and efficient synthesis of D-lyxo-phytosphingosine analogue has been achieved. The key steps involved are the Baylis-Hillman reaction of (S)-Garner aldehyde with methyl acrylate to obtain the corresponding adduct as the potential substrate, to which was added decylmagnesium bromide to obtain the E-trisubstituted alkene followed by OsO_4/NMO mediated dihydroxylation gave the desired D-lyxo-phytosphingosine analogue intermediate diol which on acid hydrolysis resulted in the formation of the target molecule in good yield.

Keywords. Baylis-Hillman acetates; decylmagnesium bromide; (S)-garner aldehyde; D-lyxo-phytosphingosine; OsO_4/NMO dihydroxylation.

1. Introduction

The Baylis-Hillman[1,2] reaction is an important atom economical carbon-carbon bond forming reaction in organic synthesis which involves the coupling of activated vinylic system and an electrophile under the catalytic influence of tertiary amines to afford multifunctional adducts. Aldehydes are the main substrate for this reaction and among them the chiral α–amino aldehydes[3] are of special interest due to the synthetic utility of the resulting adducts which have the multifunctional α-methylene-β-hydroxy-γ-amino acid moiety present in them.

Acetates of Baylis-Hillman[1,4] have been exploited as potential intermediates for the stereoselective synthesis of a variety of multifunctional molecules and natural products. Moreover, the trisubstituted alkene moiety found abundantly in various naturally occurring bioactive molecules including important antibiotics and pheromones is a key intermediate for the stereoselective synthesis of a variety of multifunctional compounds.[5] The various reported methodologies employed for stereoselective synthesis of trisubstituted alkenes from Baylis-Hillman acetates mainly includes reactions with Grignard reagent,[6] Pd-catalyzed cross-coupling reaction,[7] reaction of trialkylindium reagent,[8] Zn mediated reaction of alkyl halides in aqueous medium[5e] and Friedel-Crafts reaction.[9] Roy *et al.*[10] have recently reported the synthesis of trisubstituted alkenes *via* titanocene(III) chloride. The reaction is mediated by radically induced addition of activated bromo compounds to acetates of Baylis-Hillman adduct.

Sphingolipids are essential membrane components of all eukaryotic cells and are involved in various cellular processes such as the regulation of cell growth, adhesion, differentiation, neuronal repair and signal transduction.[11] The basic structure of a sphingolipid is composed of an aminodiol and triol backbone called sphingoid base, a polar head group (sugar, phosphate, sulphate) and a fatty acyl chain linked to amino group via amide bond. The most abundantly found sphingoid bases in nature include D-*erythro*-sphingosine, dihydrosphingosine and phytosphingosine.

Phytosphingosines (figure 1), are 2-amino-1,3,4 triol bases which are important naturally occurring bioactive sphingolipids found abundantly in plants, microorganisms and in many mammalian tissues.[12] Phytosphingosines are known to regulate cellular growth[13] and mediates the heat stress signals of yeast cells.[14] They also act as metabolic precursors for many lipid mediators.[15] Beside natural phytosphingosines, their analogues exhibit antifungal[16] and other important physiological activities such as high tumor inhibitory potency.[17] The glycosylated derivative of phytosphingosine, KRN700 is known to exhibit potent immunostimulatory properties capable of activating natural killer T (NKT) cells to produce a spectrum of cytokines.[18] Due to the biological significance of phytosphingosines and their analogues, various methodologies for

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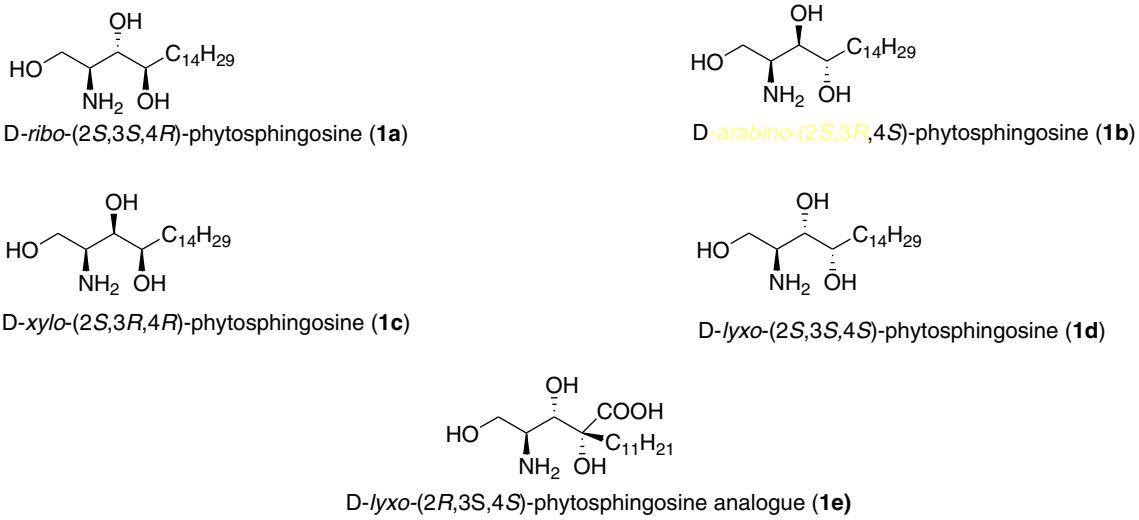


Figure 1. Phytosphingosines and D-*lyxo*-phytosphingosine analogue.

stereoselective and efficient synthesis have been developed and described in literature.[19,20]

The configurationally stable Garner aldehyde[21] has received considerable attention as an important chiral synthon for the stereoselective synthesis of phytosphingosines and their derivatives[20c,e,22] due to its inherent 2-amino-1,3-diol subunit which is the backbone of sphingolipids. The (*S*)-Garner aldehyde-methyl acrylate **3a** derived Baylis-Hillman adduct was earlier reported by Drewes *et al.*[23] as a potential intermediate for the synthesis of sphingolipid analogue. However, no work has been reported in this direction in literature for its further transformation to sphingolipids or their derivatives.

2. Experimental

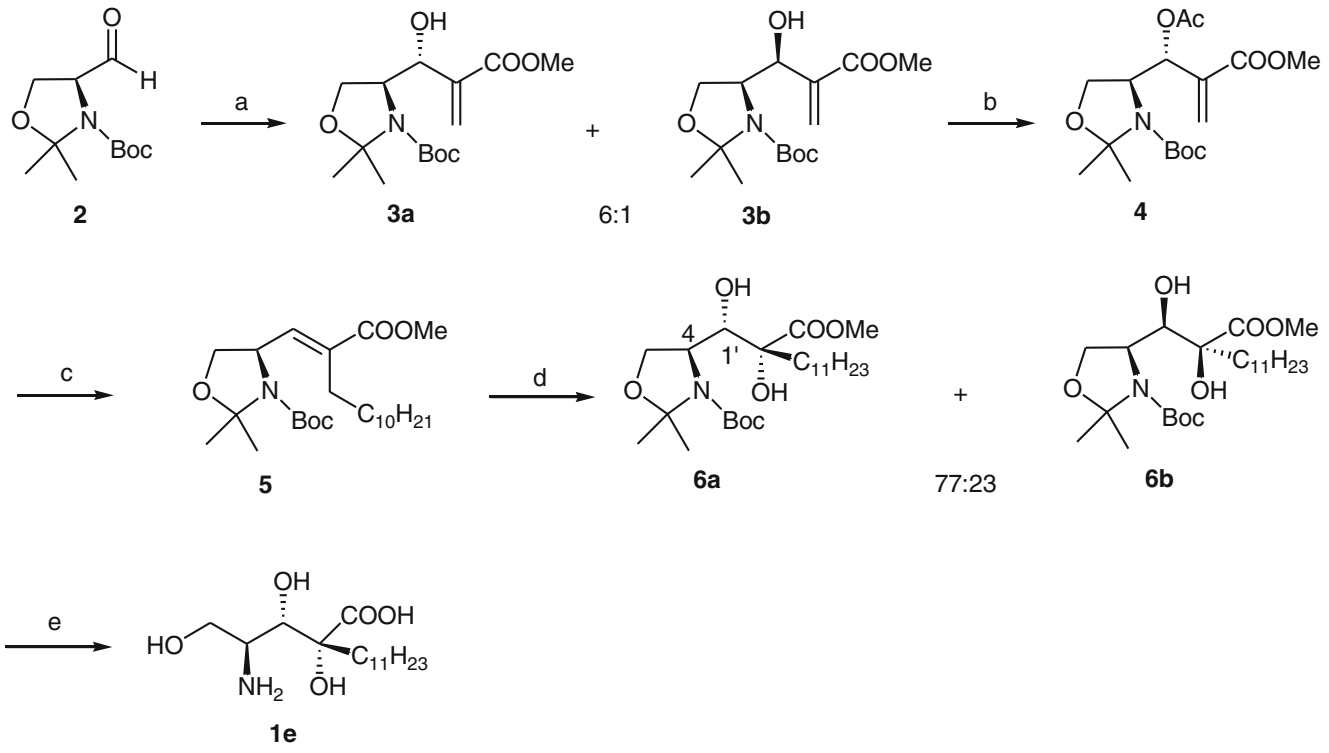
2.1 *General methods*

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance II 400 MHz spectrometer at 400 and 100 MHz, respectively. IR spectra were recorded using a Perkin-Elmer model RX 1 FT-IR spectrometer. Mass spectra were recorded on Waters Micromass q-Tof Micro spectrometer. Elemental analyses were performed using automatic Perkin Elmer 2400 CHN elemental analyzer. Optical rotations (in degrees) were recorded on Autopol-III polarimeter. The Baylis-Hillman reaction was sonicated in an ultrasonic cleaner (40 ± 5 kHz). The column chromatography was performed using silica gel (Merck, 60-120 mesh), and the flash chromatography was performed using silica gel (Merck, 230-400 mesh) by eluting with solvent indicated. All reactions were carried out using oven-dried glassware. All solvents were dried prior to use, as reported in literature.

2.2 *Procedure for synthesis of (S)-tert-butyl 4-[(R)-2-(methoxycarbonyl)-1-acetoxyallyl]-2,2-dimethylloxazolidine-3-carboxylate (**4**)*

To a stirred solution of Baylis-Hillman adduct **3a** (3.0 g, 9.52 mmol), pyridine (1.5 g, 19.0 mmol), DMAP (cat.) in dry CH_2Cl_2 (40 mL) at 0°C, acetic anhydride (1.95 g, 19.0 mmol) in dry CH_2Cl_2(15 mL) was added dropwise. The mixture was stirred at 0°C for 4 h till complete consumption of starting Baylis-Hillman adduct occurred as monitored by TLC. The mixture was poured into ice-cold water (25 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layers were washed successively with cold aqueous 5% HCl (30 mL), water (30 mL), saturated aqueous $NaHCO_3$ (30 mL), brine (30 mL) and dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure and the crude product was purified by column chromatography over silica gel (hexane: EtOAc, 89:11) to afford **4** (2.17 g, 64%) a white solid as shown inbreak scheme 1.

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41–1.62 (m, 15H), 2.14 (s, 3H), 3.76 (s, 3H), 3.78–3.86 (m, 1H), 3.95–3.98 (m, 1H), 4.23–4.40 (m, 1H), 5.86 (s, 1H), 5.93 (s, 0.43H), 6.16 (s, 0.57H), 6.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.2, 25.9, 28.3, 30.8, 52.0, 57.6, 62.9, 64.5, 70.1, 80.6, 94.9, 127.3, 137.3, 151.8, 165.0, 169.2; ESIMS m/z 380.5 (M^++ Na); Anal. Calcd. for $C_{17}H_{27}NO_7$: C, 57.12; H, 7.61; N, 3.91. Found: C, 57.05; H, 7.55; N, 3.89.



Scheme 1. Reagents and conditions: (**a**) DABCO,))))), methy acrylate 40 h, 73%, (**b**) Acetic anhydride, Pyridine, DMAP (cat.), CH_2Cl_2, 0°C, 4 h, 64%, (**c**) $C_{10}H_{21}MgBr$, THF, reflux, 5 h, 56%, (**d**) OsO_4, NMO, Me_2CO, H_2O, rt, 48 h, 65%, (e) Synthesis of D-lyxo-(2R,3S,4S)-phytosphingosine (**1e**).

2.3 *Procedure for synthesis of (R)-tert-butyl 4-[(E)-2-(methoxycarbonyl)tridec-1-enyl]-2,2-dimethyloxazolidine-3-carboxylate (**5**)*

To the stirred, freshly prepared Grignard reagent, [from decyl bromide (1.63 g. 7.36 mmol) and activated magnesium turning (0.179 g, 7.36 mmol)] in dry THF (10 mL) under nitrogen was added dropwise a solution of the acetate **4** (1.75 g, 4.90 mmol) in dry THF (10 mL) at 0°C. After addition was completed, the reaction mixture was refluxed for 5 h until TLC indicated no further change in composition of the reaction mixture. The reaction mixture was cooled to 0°C and saturated aqueous NH_4Cl solution was carefully added. The mixture was extracted with Et_2O (4 × 25 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by column chromatography over silica gel (hexane:EtOAc, 94:6) afforded **5** (1.20 g, 56%) as colorless oil as shown in scheme 1.

^{1}**H NMR** (400 MHz, $CDCl_3$): δ 0.88 (t, $J = 6.6$ Hz, 3H), 1.25–1.29 (m, 18H), 1.41–1.62 (m, 15H), 2.32–2.39 (m, 2H), 3.68–3.71 (dd, $J = 8.8$, 3.7 Hz, 1H), 3.75 (s, 3H), 4.10–4.13 (dd, $J = 8.6$, 6.8 Hz, 1H), 4.58–4.78 (m, 1H), 6.60–6.63 (d, $J = 8.7$ Hz, 1H); ^{13}**C NMR** (100 MHz, $CDCl_3$): δ 14.1, 22.6, 23.9, 26.1, 27.3, 28.7, 29.2, 30.2, 51.8, 55.1, 68.0, 80.1, 94.5, 132.9, 141.0, 151.7, 167.9; **ESIMS** *m/z* 462.3 (M^++ Na). **Anal. Calcd**. for $C_{25}H_{45}NO_5$: C, 68.30; H, 10.31; N, 3.18. Found: C, 68.23; H, 10.24; N, 3.15.

2.4 *Procedure for synthesis of (S)-tert-butyl 4-[(1S,2R)-2-(methoxycarbonyl)-1,2-dihydroxytridecyl]-2,2-dimethyloxazolidine-3-carboxylate (**6a**)*

To a stirred solution of OsO_4(4% aq. solution, 0.11 mL, 0.017 mmol) and NMO (1.12 g, 5.13 mmol) in acetone: H_2O (8:1, 15 mL) was added alkene **5** (0.750 g, 1.7 mmol) at 0°C. The mixture was stirred at room temperature for 48 h until TLC indicated complete consumption of starting material. The reaction was quenched with saturated aqueous Na_2SO_3(10 mL). The acetone was evaporated under reduced pressure. The aqueous mixture was extracted with EtOAc (4 × 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford mixture of diols **6a**:**6b** in 73:27 diastereomeric ratio as observed by ^{1}H NMR spectrum analysis of the crude mixture. Purification by column chromatography over silica gel (hexane:EtOAc, 80:20) afforded pure **6a** (0.507 g, 65%) as a colorless oil as shown in scheme 1.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 6.6 Hz, 3H), 1.23–1.29 (m, 18H), 1.41–1.65 (m, 16H),61.67–1.89 (m, 1H) 2.57 (br s, 1H), 3.50–3.65 (br s, 1H), 3.82 (s, 3H), 3.90–3.94 (dd, J = 9.7, 6.4 Hz, 1H), 4.15–4.23 (m, 2H), 4.51–4.53 (d, J = 9.8 Hz, 1H); **^{13}C NMR** (100 MHz, d_6-DMSO): δ 14.1, 23.2, 26.7, 28.4, 29.4, 31.9, 35.1, 53.0, 57.9, 63.7, 74.2, 75.3, 80.6, 93.5, 152.5, 175.5; **ESIMS** *m/z* 496.4 (M^++ Na). **Anal. Calcd**. for $C_{25}H_{47}NO_7$: C, 63.39; H, 10.00; N, 2.95. Found: C, 63.34; H, 9.94; N, 2.92.

2.5 *Procedure for synthesis of tert-butyl (2S,4R)-4-(methoxycarbonyl)-1,3,4-trihydroxypentadecan-2-ylcarbamate (**7**)*

To a solution of **6a** (0.110 g, 0.23 mmol) in MeOH (5 mL) was added Amberlyst 15 (0.155 g) and the resulting heterogeneous mixture was stirred for 48 h at room temperature till consumption of starting material occured as monitered by TLC. The mixture was passed through a small pad of celite and MeOH was evaporated under reduced pressure to afford the crude residue. Purification by coloumn chromatography over silica gel ($CHCl_3$: MeOH, 9:1) afforded **7** (0.072 g, 71%) as a colorless viscous oil as shown in scheme 2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, 3H), 1.23–1.45 (m, 27 H), 1.60–1.70 (m, 1H), 1.75–1.79 (m, 1H), 3.76–3.80 (m, 1H), 3.82 (s, 3H), 3.90–3.91 (m, 1H), 4.02–4.03 (m, 2H), 5.39–5.41(d, J = 8.4 Hz, 1H, -NH); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 22.6, 23.4, 28.3, 29.3, 29.4, 29.5, 29.6, 34.7, 51,6, 53.2, 60.4, 63.0, 79.9, 80.3, 155.6, 175.4.**Anal. Calcd**. for $C_{22}H_{43}NO_7$: C, 60.97; H, 9.93; N, 3.2. Found: C, 60.89; H, 9.90; N, 3.15.

2.6 *Procedure for synthesis of tert-butyl (4S,5S)-4-[(R)-1-(methoxycarbonyl)-1-hydroxydodecyl]-2,2-dimethyl-1,3-dioxan-5-ylcarbamate (**8**)*

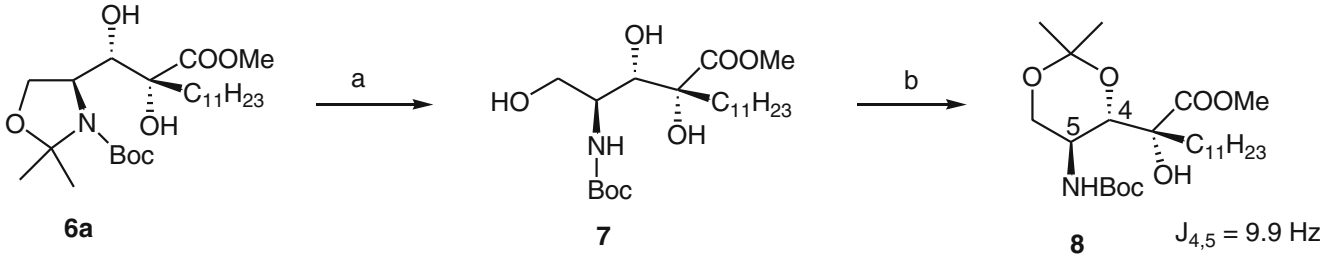
To a solution of **7** (0.045 g, 0.10 mmol) and DMP (108 mg, 1.0 mmol) in dry CH_2Cl_2(5 mL) was added PPTS (0.026 g, 0.10 mmol). The mixture was stirred for 48 h at room temperature and concentrated under reduced pressure. Purification by column chromatography over sil1ca gel (hexane:EtOAC, 84:16) afforded pure **8** (0.030, 62%) as a white solid as shown in scheme 2.

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (t, J = 6.8 Hz, 3H), 1.25–1.50 (m, 33H), 1.59–1.68 (m, 1H), 1.73–1.78 (m, 1H), 3.59–3.62 (m, 1H), 3.78 (s, 3H), 3.83–3.87 (m, 1H), 4.05–4.08 (m, 1H), 4.99-5.01 (d, $J_{4,5}$ = 9.9 Hz, 1H),5.25(s,1H,NH), 6.0(bs,1H,OH,D_2O exchangeable); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 14.1, 21.0, 22.8, 26.6, 28.5, 29.4, 29.7, 30.0, 30.9, 31.9, 52.5, 53.2, 63.5, 78.4, 79.5, 82.2, 99.3, 155.7, 172.6. **Anal. Calcd**. for $C_{25}H_{47}NO_7$: C, 63.42; H, 9.93; N, 2.93. Found: C, 63.40; H, 9.88; N, 2.9.

2.7 *Procedure for synthesis of D-lyxo-(2R,3S,4S)-phytosphingosine (**1e**)*

A solution of **6a** (0.080 g, 0.17 mmol) in 1 N HCl (6 mL) and dioxane (6 mL) was heated at 100°C with stirring for 1 h under nitrogen atmosphere. The reaction mixture was cooled to room temperature and neutralized with aqueous 1N NaOH (6 mL). The mixture was extracted with EtOAc (5 x 10 mL). The combined organic layers were washed with brine (10 mL) and dried over Na_2SO_4. Removal of solvent under reduced pressure followed by purification with flash chromatography over a short column of silica gel ($CHCl_3$:MeOH, 5:1) afforded D-*lyxo*-phtosphingosine analogue **1e** (0.039, 72%) as a white solid as shown in scheme 1.

^{1}H NMR (400 MHz, d_6-DMSO): δ 0.87 (t, J = 6.8 Hz, 3H), 1.25–1.39 (m, 17H), 1.46–1.57 (m, 2H), 1.67–1.73 (m, 1H), 3.36–3.41 (m, 1H), 3.69–3.74 (m, 1H), 3.98–4.01 (m, 1H), 4.09–4.10 (d, J = 2.0 Hz, 1H), 4.43 (br s, 3H, -OH), 7.80–8.06 (br s, 2H, -NH_2); **^{13}C NMR** (100 MHz, d_6-DMSO): δ 14.3, 22.5, 23.5, 29.6, 31.7, 35.3, 54.8, 58.5, 73.7, 79.7, 175.7. **ESIMS** *m/z* 320.5 (M^+ + 1), 302.5 (M^+ − OH). **Anal. Calcd**.



Scheme 2. Reagents and conditions: (**a**) Amberlyst 15, MeOH, rt, 48 h, 71%, (**b**) DMP, PPTS, CH_2Cl_2, rt, 48 h, 62%.

for $C_{16}H_{33}NO_5$: C, 73.48; H, 9.47; N, 3.05. Found: C, 73.39; H, 9.41; N, 3.03.

3. Results and Discussion

In continuation to our work[24] towards the synthesis of sphingolipids and their analogues and synthesis of a lactone ceramide,[24b] we have established the first, efficient and general methodology exploiting the multifunctional molecule (*S*)-Garner aldehyde-methyl acrylate derived Baylis-Hillman adduct 3a for the synthesis of D-*lyxo*-phytosphingosine analogue 1e *via* a sequence of reactions (scheme 1).

The Baylis-Hillman reaction[3g] of (*S*)-Garner aldehyde **2** with methyl acrylate in the presence of DABCO under ultrasound sonication afforded a 6:1 mixture of adducts **3a** and **3b.** The major adduct**3a** was separated by column chromatography over silica gel in 73% yield as a colorless oil. The *anti* stereochemistry has been assigned to **3a** by comparison with spectroscopic data and optical rotation value reported in literature.[3h,23] The *anti* stereochemistry of the major adduct may be rationalized on the basis of Felkin-Ahn open-chain model.[25] The adduct **3a** was converted to the corresponding acetate **4** by treating with acetic anhydride in the presence of pyridine and catalytic DMAP under standard conditions in 64% isolated yield as a white solid. Refluxing a mixture of acetate **4** with decylmagnesium bromide[6] in dry THF for 5 h under nitrogen atmosphere provided the trisubstituted alkene **5** with *E*–stereochemistry in 56% isolated yield as a colourless oil. The *E*-stereochemistry was assigned on the basis of ^{1}H NMR spectral analysis showing β-vinylic proton *cis* to the ester group appeared as a doublet, $J = 8.3$ Hz at δ 6.60–6.63 which is the characteristic peak for such Roy *et al.*[10] have recently reported the synthesis of trisubstituted alkenes via titanocene(III) chloride. The reaction is mediated by radically induced addition of activated bromo compounds to acetates of Baylis-Hillman adduct.[5e,6] The alkene **5** was screened for diastereoselective dihydroxylation with AD mix-α/ β[22e] and OsO_4/NMO dihydroxylating reagents under standard reaction conditions. No dihydroxylated product was obtained using AD mix-α or β as dihydroxylating reagent with almost complete recovery of unreacted alkene **5**. This may be due to steric hindrance around the double bond of alkene **5** which obstructs the approach of the bulky oxidation group to the double bond. However, the OsO_4/NMO catalyzed dihydroxylation of **5** proceeded quantitatively to yield a diastereomeric mixture of diols **6a** and **6b** in 77:23 ratio as observed by ^{1}H NMR spectrum analysis of the crude mixture. The major diastereomer **6a** was separated by column chromatography over silica gel in 65% yield as colourless oil. The *anti* stereochemistry of the major diol **6a** for C (4) and C (1) was established by converting it to the corresponding six membered O,O-acetonide **8** in two steps (scheme 2)[26c,27] and its ^{1}H NMR analysis.

Firstly, the oxazolidine group was removed by treatment with an acidic resin (Amberlyst 15) in MeOH to afford **7** in 71 % isolated yield as a viscous oil followed by acetalization using 2,2-dimethoxy propane and PPTS in CH_2Cl_2 to give the acetonide **8** in 62% yield as a white solid. The vicinal coupling constant of 9.9 Hz between H-5 and H-4 of acetonide **8** confirmed the *anti* stereochemistry by ^{1}H NMR spectral analysis.

Deprotection of diol **6a** under acidic conditions in 1N HCl/dioxane[28] provided crude D-*lyxo*-phytosphingosine analogue which on subsequent purification by flash column chromatography over a short column of silica gel afforded pure D-*lyxo*-phytosphingosine analogue **1e** in 72% yield as a white solid. All the compounds were characterized by ^{1}H, ^{13}C-NMR and mass spectroscopy (see supplementary information).

4. Conclusions

We have synthesized D-*lyxo*-phytosphingosine analogue **1e** by exploiting the Baylis-Hillman adduct **3a** derived acetate**4** via decylmagneisum bromide addition for the stereospecfic synthesis of *E*-trisubstituted alkene **5** and OsO_4/NMO mediated dihydroxylation as the key steps. To the best of our knowledge this is the first report for the synthesis of D-*lyxo*-phytosphingosine analogue **1e** starting from (*S*)**-**Garner aldehyde-methyl acrylate derived Baylis-Hillman adduct **3a**. The same methodology can also be applied to the synthesis of other phytosphingosine stereoisomers and their analogues.

Supplementary Information

The complete spectral data of the title compound **1e** has been included in the supplementary information (see www.ias.ac.in/chemsci).

Acknowledgements

The authors GK and AK are thankful to CSIR, New Delhi and Technical Education Quality Improvement Programme (TEQIP-II), PEC University of Technology for providing financial assistance. We are grateful to Sophisticated Analytical Instrumentation Facility (Mr.

Avtar Singh for Nuclear Magnetic Resonance), Panjab University, Chandigarh for analytical facilities.

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