Tetrahedron xxx (2009) 1–7

Contents lists available at ScienceDirect

Tetrahedron

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

# A radical mediated approach to the stereoselective formal total synthesis of (+)-Sch 642305☆

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ARTICLE INFO

*Article history:*
Received 13 May 2009
Received in revised form 14 June 2009
Accepted 16 June 2009
Available online xxx

ABSTRACT

A formal total synthesis of (+)-Sch-642305 is described. The synthesis, which commenced from a simple chiral synthon (5*S*)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one, employed, as a key step, a radical mediated opening of a chiral epoxy alcohol intermediate with $Cp_2Ti(III)Cl$ following an efficient method developed by us earlier. The resultant intermediate radical was intramolecularly trapped by the electron deficient double bond present in the molecule to give rise to its highly functionalized six-membered carbocyclic ring in stereoselective manner.



## 1. Introduction

Since the discovery of triphenylmethyl radical by Moses Gomberg, radical chemistry became a very useful tool in the arsenal of synthetic organic chemists.[1] Development of many improved methods thereafter for the generation of radicals under easy and mild conditions and the high tolerance of functional groups have made radical mediated reactions increasingly useful in the synthesis of structurally complex natural products.[2–4] The work described here is such an example which shows new perspective in Ti(III) mediated reactions for the synthesis of compounds with several chiral centres.

Our target here is Sch 642305 (**1**, Fig. 1) isolated from *Penicillium verrucosum* as a potent inhibitor of bacterial DNA primase.[5] Because DNA primase is necessary for the replication of chromosomal DNA, its inhibitors can have very useful applications as potent antimicrobials.[6,7] Jayasuriya and co-workers recently reported that Sch 642305 potently inhibits HIV-1 Tat transactivation too.[8] The functionally enriched bicyclic macrolide framework of **1**, composed of a decalactone moiety fused to a 4-hydroxycyclohexenone ring, is synthetically challenging, especially because of the additional presence of four stereogenic centres. As a result, several total syntheses of this molecule have already appeared in the literature.[9–14] We wish to report here a formal total synthesis of (+)-Sch 642305, which employs, as a key step, the radical mediated opening of chiral epoxy alcohol followed by intramolecular trapping of the resultant intermediate radical by the electron deficient double bond leading to the construction of the highly functionalized six member carbocyclic ring of the molecule.

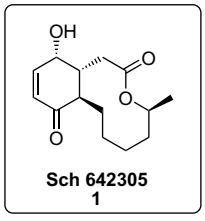
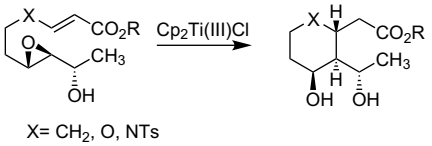



**Figure 1.**

The method has been recently developed by us for the syntheses of *trans*-fused highly substituted six member carbocycles,[15] oxacycles[16] and azacycles[17] via Ti(III) mediated chiral epoxy alcohol opening followed by 6-*exo*-*trig* mode of cyclization as shown in Scheme 1. Synthesis of (+)-Sch 642305 was undertaken to demonstrate the application of this method in the synthesis of complex natural products.




**Scheme 1.**

Our retrosynthetic approach to the synthesis of (+)-Sch 642305 is shown in Scheme 2. The principle reaction was Ti(III) mediated opening of chiral epoxy alcohol **4** followed by intramolecular trapping of the intermediate radical to lead to the cyclohexane ring of the molecule. Now compound **7** would be prepared via Wittig

☆ CDRI Communication No. 7800.

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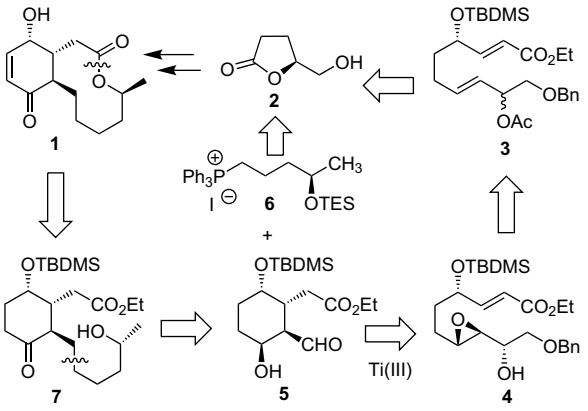
0040-4020/$ – see front matter © 2009 Published by Elsevier Ltd.
doi:10.1016/j.tet.2009.06.059



**Scheme 2.** Retrosynthetic approach.

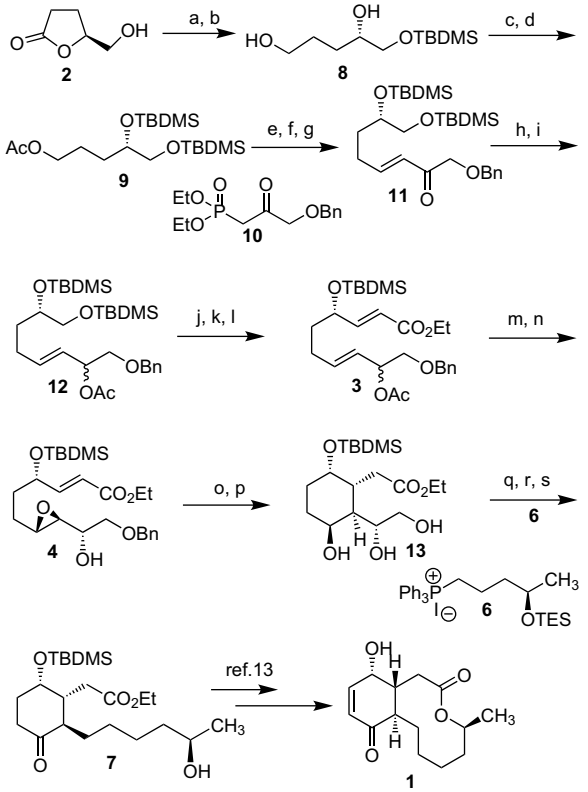
olefination from the chiral aldehyde **5** and phosphonium salt **6**. Both **5** and **6** could be synthesized from the same starting material **2**, which in turn could be synthesized from cheap commercially available starting material L-glutamic acid.[18]

## 2. Results and discussion

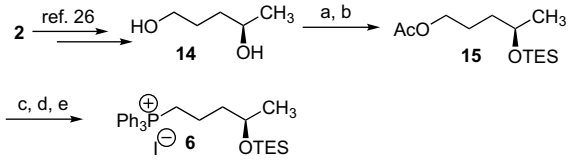
Synthesis of (+)-Sch 642305 commenced from (5*S*)-5-(hydroxymethyl)dihydrofuran-2(3*H*)-one (**2**) (see Scheme 3), which was prepared from L-glutamic acid in two steps using known methods.[18] Protection of the primary hydroxyl group as TBDMS ether, and subsequent reduction of the lactone using $LiBH_4$ furnished the diol **8**.

Chemoselective acylation of the primary hydroxyl group followed by TBDMS protection of the secondary hydroxyl group led to the formation of globally protected compound **9**. Deacylation followed by Swern oxidation[19] of the resultant primary alcohol afforded an aldehyde intermediate, which on Horner–Wadsworth–Emmons reaction with the keto-phosphonate **10**[20] afforded the desired α,β-unsaturated keto compound **11** in 75% yield. Luche reduction[21] of **11** furnished an inseperable mixture (1:1) of diastereomeric alcohols, which were protected as acetate to provide **12**. Selective deprotection of the primary TBS with HF/Py afforded a primary alcohol, which on oxidation under Dowering–Parikh[22] conditions followed by Wittig olefination with stabilized ylide $Ph_3P{=}CHCO_2Et$ afforded the formation of α,β-unsaturated ester compound **3**. $K_2CO_3$ mediated acetate deprotection of **3** set the stage for Sharpless kinetic resolution[23] of the intermediate diastereomeric mixture of allylic alcohols. L-(+)-DIPT mediated Sharpless kinetic resolution of the resultant diastereomeric allylic alcohol afforded chiral epoxy alcohol **4** in 42% yield. However, the unwanted allylic alcohol was also serviceable through recycling via Swern oxidation followed by Luche reduction. Now **4** was well equipped for implementing the crucial Ti(III) mediated epoxide opening followed by cyclization. Indeed, on exposure to the $Cp_2Ti(III)Cl$ reagent, generated in situ from $Cp_2TiCl_2$ and Zn dust and freshly fused $ZnCl_2$,[24] compound **4** underwent epoxide opening at C2 position from the hydroxy side[25] and gave rise to a radical intermediate that was intramolecularly trapped by the α,β-unsaturated ester moiety leading to the formation of the highly substituted six-membered *trans*-fused carbocyclic scaffold as the major product (along with some unidentified complex mixture of compounds as minor products), which was debenzylated to give triol moiety **13**.

Synthesis of **6**, the Wittig salt fragment, commenced from the same starting material **2** (see Scheme 4). Compound **2** was converted by reported procedure[26] into known compound **14** which could be selectively mono acylated with acetyl chloride followed by the protection of the secondary hydroxyl group as TES ether to lead to all protected compound **15**. Next **15** was transformed into **6** in three steps—selective acetyl deprotection, iodide formation and finally, Wittig salt preparation using excess TPP.



**Scheme 3.** Reagents and conditions: (a) TBDMSCl, $Et_3N$, DMAP, $CH_2Cl_2$, 0 °C to rt, 8 h, 90%; (b) $LiBH_4$, THF/$H_2O$ (20:1), 0 °C to rt, 3 h, 95%; (c) AcCl, 2,4,6-collidine, $CH_2Cl_2$, −78 °C, 7 h, 88%; (d) TBDMSOTf, 2,6-lutidine, $CH_2Cl_2$, 0 °C to rt, 5 min, 98%; (e) DIBAL-H, $CH_2Cl_2$, −78 °C, 0.5 h, 95%; (f) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −78 °C, 1.5 h; (g) $Ba(OH)_2$, THF/$H_2O$ (20:1), 2 h, 75% in two steps; (h) $NaBH_4$, $CeCl_3$, MeOH, 0 °C, 10 min, 98%; (i) $Ac_2O$, $Et_3N$, $CH_2Cl_2$, DMAP, 15 min, 95%; (j) HF/Py, THF, 0 °C to rt, 8 h, 78%; (k) $SO_3$/Py, $Et_3N$, $CH_2Cl_2$/DMSO(1:1.6), 0 °C to rt, 15 min; (l) $Ph_3P{=}CHCO_2Et$, $CH_2Cl_2$, rt, 2 h, 72% in two steps; (m) $K_2CO_3$, EtOH, 0 °C to rt, 6 h, 82%; (n) L-(+)-DIPT, $Ti(O^iPr)_4$, TBHP, $CH_2Cl_2$, MS 4 (Å), −20 °C, 2 h, 42%; (o) $Cp_2TiCl_2$, Zn, $ZnCl_2$, THF, −20 °C to rt, 48 h, 65%; (p) $H_2$/Pd(C), dry EtOAc, 24 h, 80%; (q) (i). $NaIO_4$, THF/$H_2O$ (1:1), 0 °C to rt, 6 h; (ii). $^n$BuLi, **6**, THF, −78 °C, 0.5 h, 30% in two steps (based on recovered aldehyde); (r) DMP, $NaHCO_3$, $CH_2Cl_2$, 0 °C to rt, 3 h, 70%; (s) $H_2$/Pd(C), EtOAc/EtOH (1:1), 12 h, 75%.



**Scheme 4.** Reagents and conditions: (a) AcCl, 2,4,6-collidine, $CH_2Cl_2$, −78 °C, 1.5 h, 85%; (b) TESCl, $Et_3N$, DMAP, $CH_2Cl_2$, 0 °C to rt, 10 min, 92%; (c) DIBAL-H, $CH_2Cl_2$, −78 °C, 0.5 h, 95%; (d) TPP, $I_2$, imidazole, $Et_2O$/$CH_3CN$ (4:1), 0 °C to rt, 0.5 h, 72%; (e) TPP, $K_2CO_3$, $CH_3CN$, reflux, 6 h, 75%.

Now $NaIO_4$ mediated oxidative cleavage of **13** followed by Wittig olefination with **6** led to the intermediate mixture of *cis*-*trans* olefinic alcohol which could be oxidized by Dess–Martin periodinane[27] and finally, double bond saturation and selective desilylation of TES ether were done under hydrogenation condition[28] in one pot to get the compound **7**. The spectral and analytical data of **7** were in good agreement with that reported in the literature.[13] Synthesis of **1** from **7** has already been reported.[13]

Please cite this article in press as: Chakraborty, T.K. et al., Tetrahedron (2009), doi:10.1016/j.tet.2009.06.059

## 3. Conclusions

In summary, we have accomplished the formal total synthesis of bioactive natural product (+)-Sch 642305 through a radical mediated epoxide opening followed by intramolecular cyclization strategy using $Cp_2Ti(III)Cl$ and syntheses of both the fragments commenced from the same cheap starting material. As these bicyclic macrolides are having interesting biological activities, we hope our synthetic strategy would be useful for the further investigation in the related fields.

## 4. Experimental

### 4.1. General procedures

All reactions were carried out in oven or flame-dried glassware with magnetic stirring under nitrogen atmosphere using dry, freshly distilled solvents, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, $I_2$, 7% ethanolic phosphomolybdic acid-heat and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% concd $H_2SO_4$)-heat as developing agents. Silica gel finer than 200 mesh was used for flash column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. Melting points are uncorrected. IR spectra were recorded as neat liquids or KBr pellets. Mass spectra were obtained under electron impact ionisation (EI), liquid secondary ion mass spectrometric (LSIMS) technique, electron spray ionisation (ESI) and MALDI techniques. Optical rotations were measured with a digital polarimeter. NMR spectra were recorded on 500, 400, 300 and 200 MHz spectrometers at 30 °C with 2–10 mM solutions in appropriate solvents using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in $\delta$ scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. $^{13}C$ NMR spectra were recorded on 75 and 100 MHz spectrometers with complete proton decoupling.

#### 4.1.1. (S)-5-(tert-Butyldimethylsilyloxy)pentane-1,4-diol (**8**)

$Et_3N$ (12.01 mL, 86.2 mmol) and TBDMSCl (8.445 g, 56.03 mmol) were added sequentially to a solution of compound **2**[18] (5 g, 43.1 mmol) in dry $CH_2Cl_2$ (150 mL) at 0 °C. After being stirred for 15 min at the same temperature, DMAP (525 mg, 4.3 mmol) was added and stirring was continued for 8 h with slow warming to room temperature. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution and extracted with EtOAc. The combined organic extracts were washed with water, brine, dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification of the residue by column chromatography ($SiO_2$, 15% EtOAc in petroleum ether eluant) provided pure TBDMS ether compound (8.9 g, 90 %) as a colorless oil.

$R_f$=0.5 (silica gel, 30 % EtOAc in hexane); $[\alpha]_D^{30}$ +18.1 (*c* 1.5, $CHCl_3$); IR (neat): $\nu_{max}$ 2934, 2859, 1774, 1255, 1173, 1118 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 4.52 (m, 1H), 3.82 (dd, *J*=11.2, 2.6 Hz, 1H), 3.65 (dd, *J*=11.2, 3.5 Hz, 1H), 2.54 (ddd, *J*=17.3, 10.4, 6.9 Hz, 1H), 2.40 (ddd, *J*=17.3, 9.5, 6.0 Hz, 1H), 2.30–2.09 (m, 2H), 0.87 (s, 9H), 0.05 (s, 3H), 0.045 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 177.5, 80.0, 64.8, 28.5, 25.7, 23.5, 18.2, −5.5, −5.6; (ESI): *m*/*z* (%) 248 (100) $[M+NH_4]^+$; HRMS (ESI): calcd for $C_{11}H_{22}O_3NaSi$ $[M+Na]^+$ 253.1235, found 253.1237.

Now to a solution of TBDMS ether compound (8.5 g, 36.9 mmol) in THF/$H_2O$ (100 mL:0.1 mL) at 0 °C, $LiBH_4$ (804 mg, 36.9 mmol) was added portion wise with stirring under nitrogen atmosphere and stirring was continued for 3 h at room temperature. The reaction mixture was carefully quenched with saturated aqueous $NH_4Cl$ solution at 0 °C and was extracted with EtOAc. The combined organic extracts were washed with water, brine, dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification of the residue by column chromatography ($SiO_2$, 8% EtOAc in petroleum ether eluant) provided diol compound **8** (8.2 g, 95%) as a colorless oil.

$R_f$=0.3 (silica gel, 60 % EtOAc in hexane); $[\alpha]_D^{25}$ +3.6 (*c* 5.3, $CHCl_3$); IR (neat): $\nu_{max}$ 3340, 2929, 2858, 1361, 1254 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 3.75–3.53 (m, 4H), 3.39 (dd, *J*=9.5, 8.1 Hz, 1H), 2.71 (br s, 1H), 1.79–1.20 (m, 4H), 0.91 (s, 9H), 0.08 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 71.7, 67.1, 62.2, 29.6, 28.8, 25.7, 18.1, −5.5; MS (ESI): *m*/*z* (%) 235 (95) $[M+H]^+$, 252 (85) $[M+NH_4]^+$; HRMS (ESI): calcd for $C_{11}H_{26}O_3NaSi$ $[M+Na]^+$ 257.1549, found 257.1537.

#### 4.1.2. (S)-4,5-Bis(tert-butyldimethylsilyloxy)pentyl acetate (**9**)

To the stirred solution of diol **8** (8 g, 34.18 mmol) in dry $CH_2Cl_2$ (100 mL) at −78 °C were added 2,4,6-collidine (11.9 mL, 102.54 mmol) followed by freshly distilled acetyl chloride (2.7 mL, 37.6 mmol). After being stirred for 7 h at the same temperature, it was quenched by adding saturated aqueous $NH_4Cl$ solution and extracted with EtOAc, washed with water, brine, dried ($Na_2SO_4$) and concentrated in vacuo. Column chromatography ($SiO_2$, 10% EtOAc in petroleum ether eluant) of the residue afforded pure mono acetylated compound (8.3 g, 88%) as colorless oil.

$R_f$=0.6 (silica gel, 30% EtOAc in hexane); $[\alpha]_D^{31}$ +6.2 (*c* 2.9, $CHCl_3$); IR (neat): $\nu_{max}$ 2931, 2859, 1737, 1246 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 4.08 (t, *J*=6.6 Hz, 2H), 3.68–3.55 (m, 2H), 3.38 (dd, *J*=10.3, 8.1 Hz, 1H), 2.04 (s, 3H), 1.92–1.57 (m, 2H), 1.52–1.35 (m, 2H), 0.91 (s, 9H), 0.08 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 171.0, 71.2, 67.0, 64.3, 29.1, 25.8, 24.7, 20.8, 18.2, −5.4, −5.5; MS (ESI): *m*/*z* (%) 277 (70) $[M+H]^+$, 294 (100) $[M+NH_4]^+$; HRMS (ESI): calcd for $C_{13}H_{28}O_4NaSi$ $[M+Na]^+$ 299.1654, found 299.1650.

To a solution of mono acetylated compound (8.0 g, 28.98 mmol) in $CH_2Cl_2$ (90 mL), 2,6-lutidine (6.75 mL, 57.97 mmol) and TBDMSOTf (7.3 mL, 31.88 mmol) were added sequentially at 0 °C, under nitrogen atmosphere. The reaction mixture was stirred from 0 °C to room temperature for 5 min and it was then quenched by adding saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc and the organic extracts were washed with saturated aqueous $CuSO_4$ solution, water, brine, dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification by column chromatography ($SiO_2$, 5% EtOAc in petroleum ether eluant) furnished compound **9** (11.1 g, 98%) as a colourless liquid.

$R_f$=0.7 (silica gel, 10% EtOAc in hexane); $[\alpha]_D^{24}$ −19.5 (*c* 2.8, $CHCl_3$); IR (neat): $\nu_{max}$ 2953, 2858, 1742, 1243 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 4.04 (t, *J*=6.4 Hz, 2H), 3.66 (m, 1H), 3.51 (dd, *J*=9.8, 5.3 Hz, 1H), 3.37 (dd, *J*=9.8, 6.8 Hz, 1H), 2.03 (s, 3H), 1.78–1.55 (m, 3H), 1.43 (m, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.06 (s, 6H), 0.05 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 171.1, 72.5, 66.9, 64.7, 30.5, 25.9, 25.8, 24.1, 20.9, 18.3, 18.1, −4.3, −4.8, −5.3, −5.4; MS (ESI): *m*/*z* (%) 391 (50) $[M+H]^+$, 408 (100) $[M+NH_4]^+$; HRMS (ESI): calcd for $C_{19}H_{42}O_4NaSi_2$ $[M+Na]^+$ 413.2519, found 413.2508.

#### 4.1.3. (S,E)-1-(Benzyloxy)-7,8-bis(tert-butyldimethylsilyloxy)-oct-3-en-2-one (**11**)

To a solution of compound **9** (10.0 g, 25.57 mmol) in dry $CH_2Cl_2$ (75 mL) at −78 °C, DIBAL-H (1.2 M solution in toluene, 45 mL, 53.7 mmol) was added slowly with stirring under nitrogen atmosphere. After stirring for 0.5 h, at the same temperature, the reaction mixture was quenched with dry MeOH and stirred for 0.5 h, then Na/K tartrate was added, the resulting mixture was brought to room temperature and stirred for 1 h. It was then extracted with EtOAc and extracts were washed with water, brine, dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification of the residue by column chromatography provided the deacylated product ($SiO_2$, 10% EtOAc in petroleum ether eluant, 8.45 g, 95%).

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$R_f$=0.6 (silica gel, 20% EtOAc in hexane); $[\alpha]_D^{23}$ −7.6 (*c* 1.1, $CHCl_3$); IR (neat): $\nu_{max}$ 3030, 2931, 2859, 1467, 1252 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 3.71 (m, 1H), 3.65–3.56 (m, 2H), 3.53 (dd, *J*=9.8, 5.3 Hz, 1H), 3.43 (dd, *J*=9.8, 6.8 Hz, 1H), 1.82 (br s, 1H), 1.71–1.48 (m, 4H), 0.89 (s, 18H), 0.07 (s, 6H), 0.053 (s, 3H), 0.048 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 72.5, 66.6, 62.7, 30.5, 27.8, 25.7, 25.6, 18.1, 17.8, −4.6, −5.0, −5.6, −5.7; MS (ESI): *m*/*z* (%) 349 (100) $[M+H]^+$; HRMS (ESI): calcd for $C_{17}H_{40}O_3NaSi_2$ $[M+Na]^+$ 371.2437, found 371.2410.

To a solution of oxalyl chloride (3.0 mL, 34.5 mmol) in dry $CH_2Cl_2$ (80 mL) at −78 °C, DMSO (5.2 mL, 73.57 mmol) was added slowly, in drop wise manner, with stirring under nitrogen atmosphere. After 15 min stirring, deacylated primary alcohol (8.0 g, 23 mmol, dissolved in 20 mL of dry $CH_2Cl_2$) was added to the reaction mixture. After 0.5 h of stirring at −78 °C, $Et_3N$ (16 mL, 115 mmol) was added and stirred for another 0.5 h at −78 °C and then for 0.5 h at 0 °C. The reaction mixture was then quenched with saturated aqueous $NH_4Cl$ and extracted with EtOAc. The combined organic extracts were washed with water, brine, dried ($Na_2SO_4$), filtered and concentrated in vacuo. The aldehyde thus obtained, was directly used after one flash chromatography in the next reaction, without any further characterization.

To a solution of the aldehyde and the keto phosphonate **10** (8.28 g, 27.6 mmol) in THF/$H_2O$ (100 mL:5 mL), $Ba(OH)_2 \cdot 8H_2O$ (5.4 g, 17.2 mmol) was added portion wise at 0 °C and the reaction was continued for 2 h at the same temperature. Then the reaction mixture was carefully quenched with saturated aqueous $NaHCO_3$ solution at 0 °C and filtered through sintered funnel. The filtrate was extracted with EtOAc. The combined organic extracts were washed with water, brine, dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification of the residue by column chromatography ($SiO_2$, 5% EtOAc in petroleum ether eluant) provided α,β-unsaturated keto compound **11** (8.5 g, 75%) as a colorless oil.

$R_f$=0.6 (silica gel, 10 % EtOAc in hexane); $[\alpha]_D^{25}$ −15.9 (*c* 1.2, $CHCl_3$); IR (neat): $\nu_{max}$ 2954, 2929, 2857, 1697, 1624, 1472, 1254, 1100 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.34–7.25 (m, 5H), 6.97 (dt, *J*=15.9, 6.8 Hz, 1H), 6.32 (d, *J*=15.9 Hz, 1H), 4.58 (s, 2H), 4.13 (s, 2H), 3.66 (m, 1H), 3.51 (dd, *J*=9.8, 5.3 Hz, 1H), 3.36 (dd, *J*=9.8, 6.8 Hz, 1H), 2.38–2.17 (m, 2H), 1.79–1.47 (m, 2H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (br s, 12H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 196.9, 148.9, 137.3, 129.9, 128.5, 127.9, 125.9, 73.9, 73.3, 72.2, 66.9, 32.5, 28.2, 25.9, 25.8, 18.3, 18.1, −4.3, −4.7, −5.3, −5.4; MS (ESI): *m*/*z* (%) 493 (15) $[M+H]^+$, 510 (35) $[M+NH_4]^+$; HRMS (ESI): calcd for $C_{27}H_{48}O_4NaSi_2$ $[M+Na]^+$ 515.2988, found 515.3000.

#### 4.1.4. (7S,E)-1-(Benzyloxy)-7,8-bis(tert-butyldimethylsilyloxy)-oct-3-en-2-yl acetate (**12**)

To a solution of compound **11** (8.0 g, 16.26 mmol) in dry MeOH (45 mL), $CeCl_3 \cdot 6H_2O$ (9.05 g, 24.3 mmol) was added portion wise at 0 °C under nitrogen atmosphere. Stirring was continued for 15 min at the same temperature. Then $NaBH_4$ (921 mg, 24.3 mmol) was added portion wise to the reaction mixture and the stirring was continued for 10 min. The reaction mixture was then quenched with saturated aqueous $NH_4Cl$ solution and extracted with EtOAc. The combined organic extracts were washed with water, brine, dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification of the residue by column chromatography ($SiO_2$, 10% EtOAc in petroleum ether eluant) provided the mixture of diastereomeric allylic alcohol compounds (7.87 g, 98%) as a colorless oil.

$R_f$=0.5 (silica gel, 20% EtOAc in hexane); IR (neat): $\nu_{max}$ 2929, 2857, 1463, 1253, 1108 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.35–7.22 (m, 5H), 5.74 (dt, *J*=15.3, 7.2 Hz, 1H), 5.40 (dd, *J*=15.3, 6.4 Hz, 1H), 4.56 and 4.53 (two d, *J*=12.1 Hz, 2H), 4.24 (m, 1H), 3.63 (m, 1H), 3.49 (dd, *J*=9.7, 4.8 Hz, 1H), 3.46 (dd, *J*=9.7, 3.2 Hz, 1H), 3.37 (dd, *J*=9.7, 6.4 Hz, 1H), 3.30 (t, *J*=9.7 Hz, 1H), 2.20–1.96 (m, 2H), 1.62 (m, 1H), 1.45 (m, 1H), 0.88 (s, 9H), 0.87 (s, 9H), 0.04 (s, 12H); MS (ESI): *m*/*z* (%) 512 (100) $[M+NH_4]^+$, 517 (60) $[M+Na]^+$; HRMS (ESI): calcd for $C_{27}H_{50}O_4NaSi_2$ $[M+Na]^+$ 517.3145, found 517.3135.

To a solution of diastereomeric allylic alcohol compounds (7.5 g, 15.15 mmol) in $CH_2Cl_2$ (45 mL), $Et_3N$ (6.3 mL, 45.45 mmol), $Ac_2O$ (2.1 mL, 22.7 mmol) and DMAP (183 mg, 1.5 mmol) were added sequentially at 0 °C, under nitrogen atmosphere. After stirring for 15 min at that temperature, the reaction mixture was quenched by saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic extracts were washed with water, brine, dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification by column chromatography ($SiO_2$, 5–6% EtOAc in petroleum ether eluant) furnished **12** (7.7 g, 95%) as a colorless liquid.

$R_f$=0.5 (silica gel, 10% EtOAc in hexane); IR (neat): $\nu_{max}$ 2930, 2857, 1743, 1472, 1236, 1115 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.34–7.19 (m, 5H), 5.76 (m, 1H), 5.48–5.36 (m, 2H), 4.55 and 4.49 (two d, *J*=12.8 Hz, 2H), 3.62 (m, 1H), 3.55–3.43 (m, 3H), 3.36 (dd, *J*=9.8, 6.0 Hz, 1H), 2.20–1.19 (m, 2H), 2.05 (s, 3H), 1.62 (m, 1H), 1.45 (m, 1H), 0.89 (s, 9H), 0.88 (s, 9H), 0.04 (br s, 12H); MS (ESI): *m*/*z* (%) 554 (100) $[M+NH_4]^+$; HRMS (ESI): calcd for $C_{29}H_{52}O_5NaSi_2$ $[M+Na]^+$ 559.3251, found 559.3242.

#### 4.1.5. (4S,2E,7E)-Ethyl 9-acetoxy-10-(benzyloxy)-4-(tert-butyldimethylsilyloxy)deca-2,7-dienoate (**3**)

The compound **12** was dissolved in THF (35 mL) in a plastic vial and aqueous HF/Py (1.4 mL) was added to it. The reaction mixture was stirred for 8 h at room temperature. The reaction mixture was poured into cold saturated aqueous $NaHCO_3$ solution (25 mL) and extracted with EtOAc. The organic layers were washed with water, brine, dried ($Na_2SO_4$) and concentrated in vacuo. Column chromatography ($SiO_2$, 18–20% EtOAc in petroleum ether eluant) gave pure primary alcohol compound (4.6 g, 78%) as colorless liquid.

$R_f$=0.4 (silica gel, 30% EtOAc in hexane); IR (neat): $\nu_{max}$ 3466, 2930, 2857, 1736, 1369, 1237, 1104 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.38–7.22 (m, 5H), 5.75 (m, 1H), 5.52–5.31 (m, 2H), 4.56 and 4.48 (two d, *J*=12.4 Hz, 2H), 3.68 (m, 1H), 3.58–3.33 (m, 4H), 2.30 (m, 1H), 2.16–1.97 (m, 4H), 1.66–1.49 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H); MS (ESI): *m*/*z* (%) 445 (100) $[M+Na]^+$; HRMS (ESI): calcd for $C_{23}H_{38}O_5NaSi$ $[M+Na]^+$ 445.2386, found 445.2400.

To a solution of primary alcohol (4 g, 9.46 mmol) in dry $CH_2Cl_2$ (12 mL) and dry DMSO (19 mL), $Et_3N$ (6.6 mL, 47.3 mmol) followed by $SO_3$/Py complex (7.5 g, 47.3 mmol) were added portion wise at 0 °C under nitrogen atmosphere. After 15 min of stirring at 0 °C, the reaction was quenched with saturated aqueous $NH_4Cl$ solution and extracted with EtOAc. The combined organic extracts were washed with saturated aqueous $CuSO_4$ solution, water, brine, dried ($Na_2SO_4$), and concentrated in vacuo. The aldehyde ($R_f$=0.55, 20% EtOAc in petroleum ether) thus obtained by flash chromatography was directly used for the next reaction.

To the stirred solution of the aldehyde (9.46 mmol) in $CH_2Cl_2$ (25 mL), stabilized ylide $Ph_3P{=}CHCO_2Et$ (6.6 g, 18.9 mmol) was added at room temperature under nitrogen atmosphere. After being stirred for 2 h, the reaction mixture was concentrated and the residue was purified by column chromatography ($SiO_2$, 8% EtOAc in petroleum ether eluant) to give the compound **3** (3.3 g, 72% over two steps) as a colorless oil.

$R_f$=0.7 (silica gel, 20 % EtOAc in hexane); IR (neat): $\nu_{max}$ 2934, 2857, 1721 (br), 1658, 1460, 1368, 1237 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.36–7.26 (m, 5H), 6.85 (dd, *J*=15.7, 4.8 Hz, 1H), 5.92 (d, *J*=15.7 Hz, 1H), 5.75 (m, 1H), 5.49–5.35 (m, 2H), 4.55 and 4.51 (two d, *J*=12.3 Hz, 2H), 4.30 (m, 1H), 4.19 (qd, *J*=6.8, 2.7 Hz, 2H), 3.55–3.44 (m, 2H), 2.15–2.04 (m, 2H), 2.07 (s, 3H), 1.67–1.59 (m, 2H), 1.32 (t, *J*=6.8 Hz, 3H), 0.93 (s, 9H), 0.07–0.03 (m, 6H); MS (ESI): *m*/*z* (%) 508 (100) $[M+NH_4]^+$, 513 (40) $[M+Na]^+$; HRMS (ESI): calcd for $C_{27}H_{42}O_6NaSi$ $[M+Na]^+$ 513.2648, found 513.2647.

Please cite this article in press as: Chakraborty, T.K. et al., Tetrahedron (2009), doi:10.1016/j.tet.2009.06.059

*4.1.6. (S,E)-Ethyl 6-((2S,3S)-3-((S)-2-(benzyloxy)-1-hydroxyethyl)oxiran-2-yl)-4-(tert-butyldimethylsilyloxy)-hex-2-enoate (**4**)*

The α,β-unsaturated ester compound **3** was dissolved in EtOH (20 mL) and $K_2CO_3$ (1.7 g, 12.2 mmol) was added at 0 °C under nitrogen atmosphere and stirred for 6 h. The reaction mixture was slowly allowed to come at room temperature. It was then quenched with saturated aqueous $NH_4Cl$ solution and extracted with EtOAc. The combined extracts were washed with water, brine, dried ($Na_2SO_4$), and concentrated in vacuo. Purified by column chromatography ($SiO_2$, 15% EtOAc in petroleum ether eluant) to provide allylic alcohol (2.02 g, 75%) as a colorless liquid.

$R_f$=0.5 (silica gel, 30% EtOAc in hexane); IR (neat): $\nu_{max}$ 3461, 2954, 2930, 2857, 1721, 1258, 1103 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 7.38–7.23 (m, 5H), 6.85 (dd, *J*=15.4, 4.4 Hz, 1H), 5.90 (dd, *J*=15.4, 1.5 Hz, 1H), 5.72 (dt, *J*=14.7, 6.6 Hz, 1H), 5.40 (dd, *J*=14.7, 5.1 Hz, 1H), 4.54 (s, 2H), 4.37–4.10 (m, 4H), 3.44 (dd, *J*=9.5, 3.7 Hz, 1H), 3.28 (dd, *J*=9.5, 8.1 Hz, 1H), 2.16–2.01 (m, 2H), 1.70–1.56 (m, 2H), 1.31 (t, *J*=7.3 Hz, 3H), 0.91 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); MS (ESI): *m*/*z* (%) 466 (100) $[M+NH_4]^+$; HRMS (ESI): calcd for $C_{25}H_{40}O_5NaSi$ $[M+Na]^+$ 471.2542, found 471.2531.

To a suspension of activated 4 Å MS (340 mg, 20 mol%) in $CH_2Cl_2$ (10 mL), $Ti(O^iPr)_4$ (1.12 mL, 3.78 mmol) and L-(+)-DIPT (0.96 mL, 4.55 mmol) were added sequentially at −20 °C under nitrogen atmosphere. After 20 min of stirring, a solution of diastereomeric mixture of allylic alcohols (1.7 g, 3.78 mmol) in $CH_2Cl_2$ (5 mL) was added and stirring continued for 30 min at the same temperature. Then TBHP (3.46 M in toluene, 1.27 mL, 4.38 mmol) was added to the reaction mixture and stirred for another 1.5 h at −20 °C. The reaction was quenched with $H_2O$ (50 mL) and temperature was allowed to come to 0 °C and vigorously stirred for 1 h. Then it was extracted with EtOAc. The combined organic extracts were washed with water, brine, dried ($Na_2SO_4$), and concentrated in vacuo. Purified by column chromatography ($SiO_2$, 15% EtOAc in petroleum ether eluant) to provide the pure chiral epoxy alcohol compound **4** (739 mg, 42%) as a colorless liquid.

$R_f$=0.5 (silica gel, 30% EtOAc in hexane); $[\alpha]_D^{25}$ −11.4 (*c* 1.1, $CHCl_3$); IR (neat): $\nu_{max}$ 3473, 2931, 2858, 1717, 1657, 1461, 1365, 1260 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 7.38–7.27 (m, 5H), 6.84 (dd, *J*=15.4, 4.4 Hz, 1H), 5.93 (dd, *J*=15.4, 1.5 Hz, 1H), 4.57 (s, 2H), 4.38 (m, 1H), 4.19 (q, *J*=7.4 Hz, 2H), 3.66 (m, 1H), 3.60–3.49 (m, 2H), 2.92 (m, 1H), 2.77 (dd, *J*=5.1, 2.2 Hz, 1H), 1.76–1.48 (m, 4H), 1.32 (t, *J*=6.6 Hz, 3H), 0.93 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 166.5, 150.1, 137.6, 128.4, 127.8, 127.7, 120.4, 73.5, 71.3, 70.8, 69.5, 60.4, 58.0, 55.9, 33.1, 26.6, 25.8, 18.1, 14.2, −4.6, −4.9; MS (ESI): *m*/*z* (%) 465 (10) $[M+H]^+$, 482 (100) $[M+NH_4]^+$; HRMS (ESI): calcd for $C_{25}H_{40}O_6NaSi$ $[M+Na]^+$ 487.2491, found 487.2481.

*4.1.7. Ethyl 2-((1R,2R,3S,6S)-6-(tert-butyldimethylsilyloxy)-2-((R)-1,2-dihydroxyethyl)-3-hydroxycyclohexyl)acetate (**13**)*

Activated Zn powder (507 mg, 7.75 mmol), freshly fused $ZnCl_2$ (524 mg, 3.87 mmol) and $Cp_2TiCl_2$ (963 mg, 3.87 mmol) were taken in dry THF (35 mL) and stirred for 0.5 h at room temperature. The color of the reaction mixture turned into deep green. Then it was cooled to −20 °C and epoxy alcohol **4** (600 mg, 1.29 mmol) in dry THF (10 mL) was added. The reaction mixture was allowed to come at room temperature slowly. Then it was stirred for 48 h. Reaction was quenched with saturated aqueous $NH_4Cl$ solution and extracted with EtOAc. The combined organic layer was washed with $H_2O$, brine, dried ($Na_2SO_4$) and concentrated in vacuo. Purification by column chromatography ($SiO_2$, 25% EtOAc in petroleum ether eluant) provided the 1,3-diol as pure gummy liquid (391 mg, 65%).

$R_f$=0.5 (silica gel, 30 % EtOAc in hexane); $[\alpha]_D^{24}$ +26.5 (*c* 1.1, $CHCl_3$); IR (neat): $\nu_{max}$ 3442, 2930, 2857, 1732, 1252, 1106, 1038 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 7.39–7.29 (m, 5H), 4.63 and 4.53 (two d, *J*=12.5 Hz, 2H), 4.22–4.08 (m, 3H), 4.03–3.88 (m, 3H), 3.86–3.68 (m, 2H), 3.61 (dd, *J*=9.5, 5.1 Hz, 1H), 2.58 (m, 1H), 2.38 (dd, *J*=8.8, 5.5 Hz, 2H), 1.98 (m, 1H), 1.85–1.40 (m, 4H), 1.27 (t, *J*=7.3 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 175.1, 128.4, 127.7, 127.6, 73.5, 72.4, 71.3, 70.9, 67.1, 60.9, 40.6, 36.2, 33.6, 27.3, 26.7, 25.9, 18.1, 14.1, −4.2, −5.1; MS (ESI): *m*/*z* (%) 467 (80) $[M+H]^+$, 484 (100) $[M+NH_4]^+$; HRMS (ESI): calcd for $C_{25}H_{42}O_6NaSi$ $[M+Na]^+$ 489.2648, found 489.2635.

The 1,3-diol (300 mg, 0.64 mmol) was dissolved in dry EtOAc (6 mL) and 10% Pd on charcoal (30 mg) was added and subjected to hydrogenation under atmospheric pressure using a $H_2$-filled balloon. After 24 h, the reaction mixture was filtered through a short pad of Celite and the filter cake was washed with EtOAc. The filtrate and washings were combined, concentrated in vacuo and purified by column chromatography ($SiO_2$, 70% EtOAc in petroleum ether eluant) to provide the pure triol compound **13** (193 mg, 80%) as a gummy liquid.

$R_f$=0.3 (silica gel, 70% EtOAc in hexane); $[\alpha]_D^{24}$ +32.0 (*c* 1.5, $CHCl_3$); IR (neat): $\nu_{max}$ 3446, 2930, 1734, 1473, 1075 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): δ 4.32–4.07 (m, 4H), 3.95 (br s, 2H), 3.86 (m, 1H), 3.75–3.50 (m, 2H), 2.52 (m, 1H), 2.36 (dd, *J*=6.6, 3.7 Hz, 2H), 1.99 (m, 1H), 1.83–1.40 (m, 4H), 1.30 (t, *J*=6.6 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 175.4, 72.9, 71.2, 67.5, 65.1, 61.0, 40.9, 36.3, 33.7, 27.2, 26.7, 25.8, 18.1, 14.1, −4.3, −5.1; MS (ESI): *m*/*z* (%) 377 (100) $[M+H]^+$, 394 (90) $[M+NH_4]^+$; HRMS (ESI): calcd for $C_{18}H_{36}O_6NaSi$ $[M+Na]^+$ 399.2178, found 399.2181.

*4.1.8. (R)-4-(Triethylsilyloxy)pentyl acetate (**15**)*

To the stirred solution of diol **14**[26] (1.3 g, 12.5 mmol) in dry $CH_2Cl_2$ (40 mL) at −78 °C were added 2,4,6-collidine (4.37 mL, 37.5 mmol) followed by freshly distilled acetyl chloride (0.97 mL, 13.75 mmol). After being stirred for 1.5 h at the same temperature, it was quenched by adding saturated aqueous $NH_4Cl$ solution and extracted with EtOAc, washed with water, saturated $CuSO_4$ solution, brine, dried ($Na_2SO_4$) and concentrated in vacuo. Column chromatography ($SiO_2$, 20% EtOAc in petroleum ether eluant) of the residue afforded pure mono acetylated compound (1.55 g, 85%) as colorless oil.

$Et_3N$ (2.67 mL, 19.18 mmol) and TESCl (2.42 mL, 14.4 mmol) were added sequentially to a solution of mono acetylated compound (1.4 g, 9.6 mmol) in dry $CH_2Cl_2$ (40 mL) at 0 °C. After being stirred for 5 min at the same temperature, DMAP (117 mg, 0.96 mmol) was added and stirring was continued for 10 min with slow warming to room temperature. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution and extracted with EtOAc. The combined organic extracts were dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification of the residue by column chromatography ($SiO_2$, 3–5% EtOAc in petroleum ether eluant) provided pure TES ether compound **15** (2.3 g, 92 %) as a colorless oil.

$R_f$=0.6 (silica gel, 10% EtOAc in hexane); $[\alpha]_D^{24}$ −11.9 (*c* 2.6, $CHCl_3$); IR (neat): $\nu_{max}$ 2956, 2877, 1743, 1236, 1045, 1007 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): δ 4.03 (t, *J*=6.8 Hz, 2H), 3.82 (sextet, *J*=6.0 Hz, 1H), 2.03 (s, 3H), 1.78–1.50 (m, 2H), 1.53–1.40 (m, 2H), 1.14 (d, *J*=6.0 Hz, 3H), 0.96 (t, *J*=7.5 Hz, 9H), 0.58 (q, *J*=7.5 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): δ 171.1, 67.9, 64.6, 35.8, 24.9, 23.7, 20.9, 6.8, 4.9; MS (ESI): *m*/*z* (%) 283 (80) $[M+Na]^+$; HRMS (ESI): calcd for $C_{13}H_{28}O_3NaSi$ $[M+Na]^+$ 283.1705, found 283.1715.

*4.1.9. (R)-Triphenyl(4-(triethylsilyloxy)pentyl)phosphonium iodide (**6**)*

To a solution of compound **15** (2.2 g, 8.44 mmol) in dry $CH_2Cl_2$ (35 mL) at −78 °C, DIBAL-H (1.2 M solution in toluene, 15.5 mL, 18.56 mmol) was added slowly with stirring under nitrogen atmosphere. After stirring for 0.5 h, at the same temperature, the reaction mixture was quenched with dry MeOH and stirred for

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0.5 h. Then Na/K tartrate was added and the resulting mixture was brought to room temperature and stirred for 1 h. It was then extracted with EtOAc and extracts were washed with water, brine, dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification of the residue by column chromatography provided the deacylated product ($SiO_2$, 12–13% EtOAc in petroleum ether eluant, 1.75 g, 95%).

$R_f$=0.5 (silica gel, 30 % EtOAc in hexane); $[\alpha]_D^{31}$ −8.5 (*c* 1.4, $CHCl_3$); IR (neat): $\nu_{max}$ 3336, 2953, 2876, 1048, 1005 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 3.89 (sextet, *J*=6.0 Hz, 1H), 3.68–3.52 (m, 2H), 1.94 (br s, 1H), 1.68–1.47 (m, 4H), 1.16 (d, *J*=6.0 Hz, 3H), 0.96 (t, *J*=8.3 Hz, 9H), 0.60 (q, *J*=8.3 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 68.2, 63.0, 36.1, 28.4, 23.2, 6.8, 4.8; MS (ESI): *m*/*z* (%) 241 (100) $[M+Na]^+$; HRMS (ESI): calcd for $C_{11}H_{26}O_2NaSi$ $[M+Na]^+$ 241.1623, found 241.1618.

To a solution of primary alcohol in dry $Et_2O/CH_3CN$ (16 mL:4 mL), imidazole (1.87 g, 27.52 mmol) was added slowly with stirring at 0 °C under nitrogen atmosphere. Then TPP (2.7 g, 10.32 mmol) followed by $I_2$ (1.83 g, 7.224 mmol) were added to the reaction mixture at the same temperature. After being stirred for next 0.5 h, it was quenched with saturated $NaHCO_3$ solution and extracted with EtOAc, water, brine, dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification of the residue by fast column chromatography provided the primary iodide product ($SiO_2$, only petroleum ether eluant, 1.62 g, 72%) which was directly used for the next reaction without further characterization.

The primary iodide (1.5 g, 4.57 mmol) was immediately taken in dry $CH_3CN$ (20 mL) and TPP (3.6 g, 13.72 mmol) followed by $K_2CO_3$ (3.15 g, 22.85 mmol) were added to the reaction mixture. The reaction mixture was refluxed for 6 h, then cooled to room temperature and filtered through cotton to remove the $K_2CO_3$. Then it was concentrated in vacuo. Purification of the residue by column chromatography ($SiO_2$, 4% MeOH in $CHCl_3$ eluant) provided the solid Wittig salt **6** as a yellow solid (2.02 g, 75%).

$R_f$=0.3 (silica gel, 10 % MeOH in $CHCl_3$); $[\alpha]_D^{26}$ −1.8 (*c* 2.9, $CHCl_3$); IR (neat): $\nu_{max}$ 3405, 3051, 2955, 2876, 1437, 1341, 1112, 1009 $cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta$ 7.90–7.65 (m, 15H), 4.01 (m, 1H), 3.82 (m, 1H), 3.51 (m, 1H), 2.06–1.61 (m, 4H), 1.10 (d, *J*=6.0 Hz, 3H), 0.81 (t, *J*=7.5 Hz, 9H), 0.44 (qd, *J*=7.5, 3.0 Hz, 6H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta$ 135.0 (d, $J_{P-C}$=2.2 Hz), 133.5 (d, $J_{P-C}$=9.9 Hz), 130.4 (d, $J_{P-C}$=12.6 Hz), 118.0 (d, $J_{P-C}$=85.8 Hz), 67.7, 39.7 (d, $J_{P-C}$=15.4 Hz), 23.7, 22.9 (d, $J_{P-C}$=50.1 Hz), 18.9 (d, $J_{P-C}$=3.8 Hz), 6.7, 4.8; MS (ESI): *m*/*z* (%) 464 (100) $[M+H]^+$; HRMS (ESI): calcd for $C_{29}H_{40}OSiP$ $[M]^+$ 463.2586, found 463.2605.

#### 4.1.10. Ethyl 2-((1R,2R,6S)-6-(tert-butyldimethylsilyloxy)-2-((R)-5-hydroxyhexyl)-3-oxocyclohexyl)acetate (7)

A solution of the triol **13** (100 mg, 0.26 mmol) in THF:$H_2O$ (1:1, 2.0 mL) was treated with $NaIO_4$ (114 mg, 0.53 mmol) at 0 °C. After 6 h stirring from 0 °C to room temperature, the reaction mixture was extracted with $CH_2Cl_2$. The combined organic extracts were washed with water, brine, dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification by flash column chromatography ($SiO_2$, 30% EtOAc in petroleum ether eluant) afforded the aldehyde compound as a white gummy liquid.

Now $^n$BuLi solution in hexane (1.6 M, 0.36 mL) was added to the solution of the Wittig salt **6** (383 mg, 0.65 mmol) in freshly dried THF at −78 °C under nitrogen atmosphere. It was stirred for 30 min at the same temperature and the colour of the solution changed into reddish yellow. Next the aldehyde in THF was added to the reaction mixture and allowed to warm up to 0 °C with continuous stirring. The reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution and extracted with EtOAc. The combined organic extracts were dried ($Na_2SO_4$), filtered and concentrated in vacuo. Purification of the residue by column chromatography ($SiO_2$, 8 % EtOAc in petroleum ether eluant) provided the mixture of *cis* and *trans* olefinic compounds (42 mg, 30% based on recovered starting material) as a colorless oil. ($R_f$=0.5, 20% EtOAc in petroleum ether).

To a stirred solution of olefins (15 mg, 0.028 mmol) in $CH_2Cl_2$ (2 mL), $NaHCO_3$ (14 mg, 0.17 mmol) followed by Dess–Martin periodinane (59 mg, 0.14 mmol) were added at 0 °C under nitrogen atmosphere, then allowed to come to room temperature and stirred for 3 h. Saturated $Na_2S_2O_3$ solution were added and the biphasic mixture was stirred for 15 min and extracted with EtOAc. The organic extracts were washed with saturated $NaHCO_3$ solution, water, brine, dried ($Na_2SO_4$) and concentrated in vacuo. The keto compound ($R_f$=0.6, 20% EtOAc in petroleum ether), thus obtained in 70% yield, was directly used after flash chromatography for the next reaction without further characterization.

To a solution of the mixture of olefinic-keto compound (10 mg, 0.018 mmol) in dry EtOH (1 mL), 10% Pd/C (catalytic) was added and the mixture was hydrogenated and selectively TES ether was deprotected using a $H_2$-filled balloon for 12 h. It was then filtered through a short pad of Celite and the filter cake was washed with EtOAc. The filtrate and washings were combined and concentrated in vacuo. Purification by column chromatography ($SiO_2$, 30% EtOAc in petroleum ether eluant) eluted compound **7** (5.8 mg, 75%) as colorless oil.

$R_f$=0.4 (silica gel, 40 % EtOAc in hexane); in literature[13] $[\alpha]_D$ for **7** +19.3 (*c* 0.6, $CHCl_3$), observed $[\alpha]_D^{31}$ +22.2 (*c* 0.05, $CHCl_3$); IR (neat): $\nu_{max}$ 3338, 2924, 2855, 1734, 1714 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta$ 4.16 (m, 1H), 4.14 (q, *J*=6.9 Hz, 2H), 3.79 (m, 1H), 2.62 (td, *J*=12.8, 6.9 Hz, 1H), 2.56 (dd, *J*=16.7, 8.8 Hz, 1H), 2.45 (m, 1H), 2.37–2.20 (m, 3H), 2.00 (m, 1H), 1.84 (m, 1H), 1.60–1.55 (m, 2H), 1.5–1.39 (m, 3H), 1.35–1.24 (m, 3H), 1.28 (t, *J*=7.0 Hz, 3H), 1.17 (d, *J*=6.9 Hz, 3H), 0.92 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); MS (ESI): *m*/*z* (%) 437 (100) $[M+Na]^+$; HRMS (ESI): calcd for $C_{22}H_{42}O_5NaSi$ $[M+Na]^+$ 437.2699, found 437.2682.

## Acknowledgements

The authors wish to thank DST, New Delhi for the Ramanna Fellowship (SR/S1/RFOC-06/2006; T.K.C.) and CSIR, New Delhi for the research fellowships (R.S. and P.K.R).

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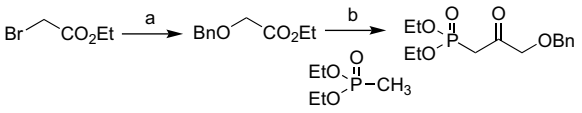


***Reagents and conditions***: (a) BnOH, NaH, THF, TBAI, 0 °C to rt, 12 h, 70%; (b) $^{n}$BuLi, THF, -78 °C- 0 °C, 2 h, 85%.

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Please cite this article in press as: Chakraborty, T.K. et al., Tetrahedron (2009), doi:10.1016/j.tet.2009.06.059