DOI: 10.1002/ejoc.200700868

An Efficient Total Synthesis of Decarestrictine D[‡]

Priti Gupta[a] and Pradeep Kumar*[a]

Keywords: Macrolides / Hydrolytic kinetic resolution / Sharpless asymmetric dihydroxylation / Cross metathesis / Ring-closing metathesis

An efficient total synthesis of decarestrictine D has been achieved using cross-metathesis or ring-closing metathesis and Yamaguchi macrolactonization as key steps. The stereogenic centres were generated by means of hydrolytic kinetic resolution (HKR) and Sharpless asymmetric dihydroxylation (AD).

Introduction

Decarestrictine D (**1a**), a 10-membered ring lactone was isolated independently from *Penicillium corylophilum*, *P. simplicissimum*[1] and from the Canadian Tuchahoe fungi *Polyporus tuberaster*.[2] It shows inhibitory activity against cholesterol biosynthesis at 10^{-7} M, in HEP-G2 liver cell.[1a] The structural difference between **1a** and the well known HMG-CoA inhibitors such as mevinolin, compactin and other synthetic cholesterol-lowering agent suggests a different mode of action operative with **1a**. In addition, **1a** is highly selective in that it exhibits no significant antibacterial, antifungal, antiprotozoal or antiviral activity.[1,2] Other members of this 10-membered ring lactone family include decarestrictine A (**1b**), decarestrictine B (**1c**) and decarestrictine C (**1d**) (Figure 1). Considering its strong and selective biological profile, decarestrictine D has attracted a great deal of interest among synthetic organic chemists worldwide as an attractive synthetic target towards developing new cholesterol-lowering drugs. Consequently, the synthesis of **1a** and its seco-acid have been reported by various research groups.[3–7] The synthetic approaches described so far for **1a** involve either a chiral building block, asymmetric catalysis or a chiral induction to establish one or more of stereogenic centres present in the molecule. However, synthetic strategies that are based on 1,3-chiral induction to establish the C7 stereocentre suffer from low diastereoselectivity.[3,7] Similarly the Sharpless AD reaction of a diene[3] to generate the C3 and C4 stereocentres and stereoselective reduction of a keto group by L-selectride[6] to establish the C4 stereocentre were found to give a mixture of two regioisomers and stereoisomers, respectively.

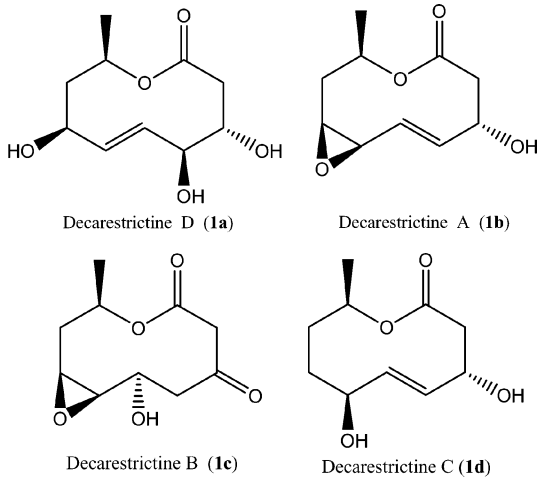


Figure 1. Examples of 10-membered ring lactones.

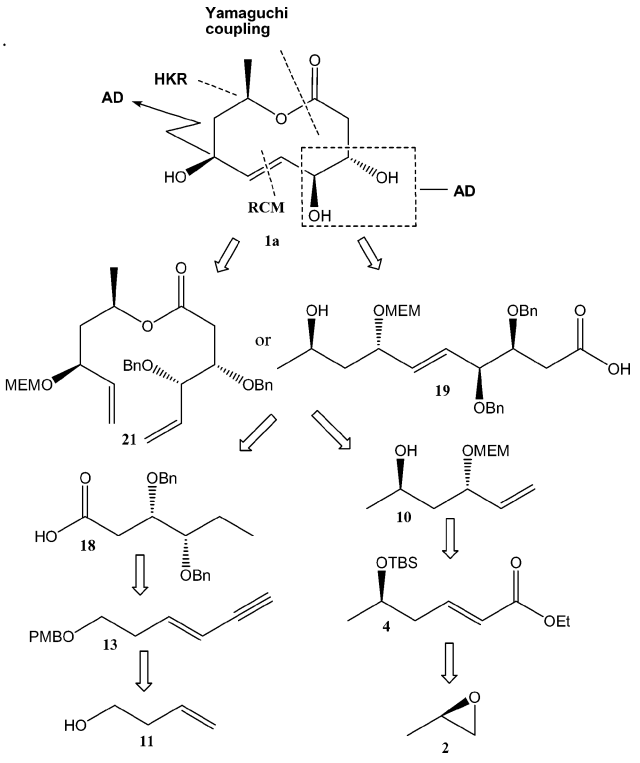
Pilli's synthesis also suffers from use of excess of the toxic Cr reagent coupled with a mixture of two diastereomers at C7 centre. In addition, the majority of the approaches known for decarestrictine D are based on macrolactonization for the key macrocyclization and suffer from low yields (17–45%) for the target molecule.[3,5,6] As a part of our research programme aimed at developing enantioselective synthesis of naturally occurring lactones[8] and amino alcohols[9] we became interested in devising a simple and practical route to decarestrictine D. Herein we report our successful endeavors towards the total synthesis of **1a** employing hydrolytic kinetic resolution (HKR), Sharpless asymmetric dihydroxylation (AD), Yamaguchi coupling, cross metathesis and ring-closing metathesis (RCM) as the key steps.

Results and Discussion

Our retrosynthetic analysis is based on convergent approach as outlined in Scheme 1. We envisioned that the

[‡] This is NCL communication no. 6706.
[a] Division of Organic Chemistry, National Chemical Laboratory, Pune 411008, India
Fax: +91-20-25902629
E-mail: pk.tripathi@ncl.res.in

ring-closing could be effected by Yamaguchi macrolactonization of the *seco*-acid **19** or by ring-closing metathesis of diene **21**. *seco*-Acid **19** in turn could be derived from cross-metathesis of alcohol **10** and acid **18**. Diene **21** could be prepared by Yamaguchi coupling of the same fragments **10** and **18**. Both the fragments **10** and **18** could be obtained from olefins **4** and **13**, respectively, via AD. Olefins **4** and **13** in turn could be derived from the commercially available propylene oxide and 3-butene-1-ol, respectively.



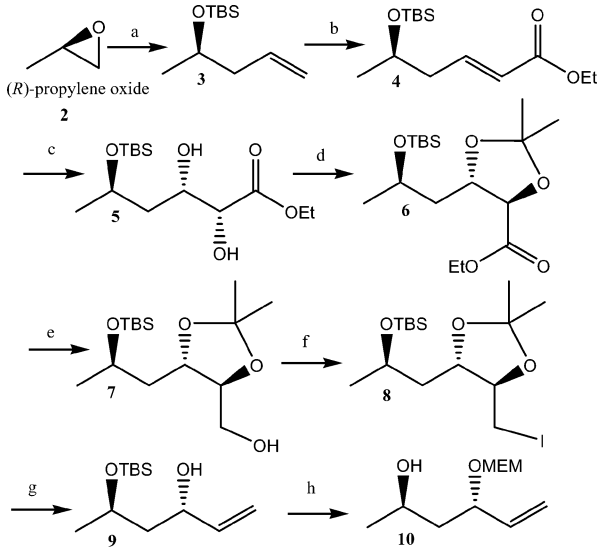
Scheme 1. Retrosynthetic route to decarestrictine D.

Synthesis of Alcohol 10

The synthesis of alcohol **10** started from commercially available propylene oxide (Scheme 2). Thus, racemic propylene oxide was resolved by using *R*,*R*-salen-Co^{III}OAc to give (*R*)-propylene oxide **2**.[10]

The ring opening of (*R*)-propylene oxide **2** with vinylmagnesium bromide followed by protection of hydroxy group as TBS ether gave the olefin **3** in 94% yield. The olefin **3** on cross-metathesis[11] with ethyl acrylate using Grubbs' second-generation catalyst afforded the *trans*-olefin **4** in 80% yield. The olefin **4** was treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2$PHAL under AD conditions[12] to give the diol **5** in 96% yield with >95% *de*.[13]

Treatment of diol with 2,2-dimethoxypropane in the presence of catalytic amount of *p*TSA (**5**→**6**) followed by reduction using DIBAL-H provided the alcohol **7** in 94% yield. Alcohol **7** was converted into iodo **8** in 87% yield, followed by reductive elimination using Zn/EtOH to give



Scheme 2. Synthesis of alcohol **10**: (a) (i) vinylmagnesium bromide, THF, CuI, –20 °C, 12 h, 89%; (ii) TBDMS-Cl, imidazole, CH_2Cl_2, 0 °C to room temp., 4 h, 94%; (b) Ethyl acrylate, $RuCl_2$(=CHPh)-(PCy_3)(IEMS), benzene, room temp., 20 h, 80%; (c) $(DHQ)_2$-PHAL, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1 M in toluene), *t*BuOH/H_2O (1:1), 0 °C, 24 h, 96%; (d) *p*TSA, 2,2-DMP, CH_2Cl_2, 2 h, 89%; (e) DIBAL-H, CH_2Cl_2, 0 °C to room temp., 2 h, 94%; (f) (i) TsCl, Et_3N, CH_2Cl_2, 2 h; (ii) NaI, 2-butanone, reflux, 6 h, 87% for both steps; (g) Zn, EtOH, reflux, 8 h, 94%; (h) (i) MEMCl, DIPEA, CH_2Cl_2, 8 h; (ii) TBAF, THF, 6 h, 75% for both steps.

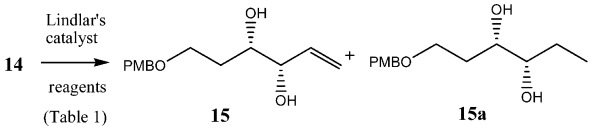
the allylic alcohol **9** in 94% yield. Alcohol **9** was protected as MEM ether followed by subsequent TBS deprotection to give the required alcohol fragment **10** in 75% yield from both the steps.

Synthesis of Acid 18

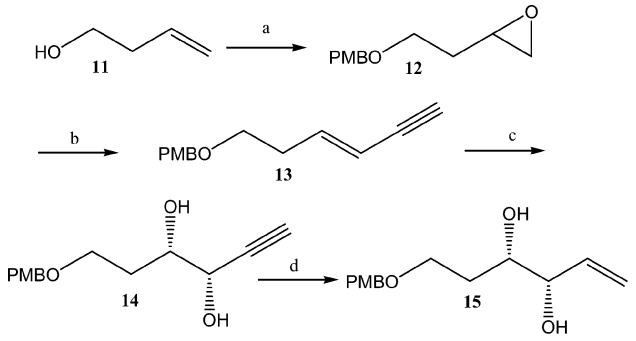
The synthesis of acid fragment **18** commenced from commercially available 3-butene-1-ol **11**. In order to generate the *trans*-olefin to execute the AD, 3-butene-1- ol was converted into the enyne moiety. Thus, protection of alcohol **11** with PMB bromide in the presence of NaH followed by oxidation using *m*CPBA gave epoxide **12** in 96% yield. Ring opening of epoxide **12** with lithium acetylide in DMSO followed by hydroxy group protection as mesyl and subsequent elimination using DBU afforded the enyne **13** in 82% yield. The enyne **13** was further treated with osmium tetroxide and potassium ferricyanide as co-oxidant in the presence of $(DHQ)_2$PHAL under AD conditions to give the diol **14** in 94% yield with 94% *ee*.[14]

The partial hydrogenation of **14** proved to be challenging. Irrespective of whether catalytic quantity or several molar equivalent of quinoline were present, the mixture of **15** and overhydrogenated product **15a** was formed (Table 1). However, the use of 1-octene as a co-solvent along with EtOAc in the presence of pyridine (EtOAc/pyridine/1-octene = 10:1:1) furnished the olefinic diol **15** as a single product in 94% yield (Scheme 3).

Table 1. Partial hydrogenation of **14**.

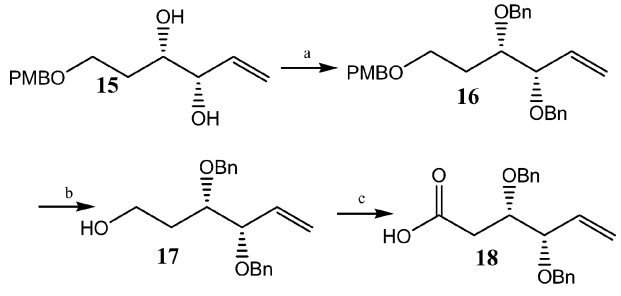


Entry	Base	Solvents	**15**:**15a**
1	quinoline (catalytic)	EtOAc	0:100
2	quinoline (10 equiv.)	EtOAc	10:90
3	quinoline (10 equiv.)	benzene	30:70
4	pyridine	octene/EtOAc (1:10)	100:0



Scheme 3. Synthesis of diol **14**: (a) (i) PMBBr, NaH, TBAI, THF, 0 °C to room temp., 2 h, 93%; (ii) *m*-CPBA, CH_2Cl_2, 0 °C to room temp., 8 h, 96%; (b) (i) LiC≡CH/ethylenediamine, DMSO, 0 °C to room temp., overnight, 89%; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C to room temp., 2 h; (iii) DBU, toluene, reflux, 4 h, 82% from two steps; (c) $(DHQ)_2PHAL$, K_2CO_3, $K_3Fe(CN)_6$, $MeSO_2NH_2$, OsO_4 (0.1 M in toluene), *t*BuOH/H_2O (1:1), 0 °C, 24 h, 94%; (d) Lindlar's catalyst, pyridine/octene/EtOAc (1:1:10), 2 h, 94%.

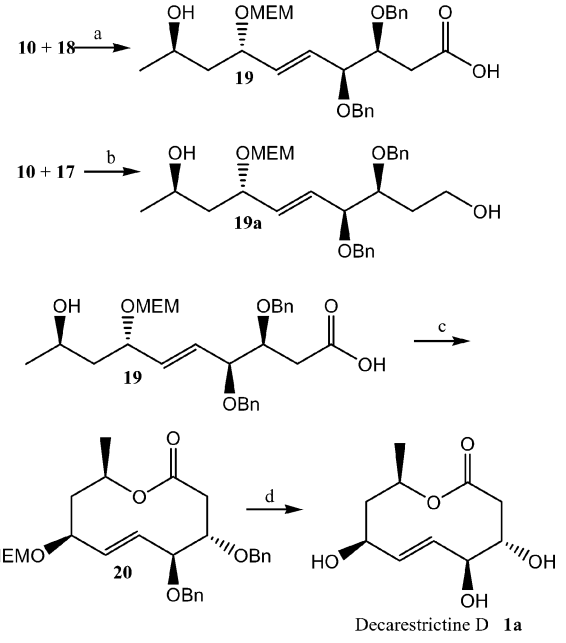
The treatment of diol **15** with BnBr in the presence of NaH gave dibenzyl olefin **16** which on PMB deprotection by using DDQ furnished the alcohol **17**[15] in 93% yield. The alcohol **17** was oxidised to aldehyde by using IBX followed by subsequent oxidation using $NaClO_2$ to give the required acid fragment **18** in 80% yield (Scheme 4).



Scheme 4. Synthesis of acid **18**: (a) BnBr, NaH, THF, 0 °C to room temp., 4 h, 85%; (b) DDQ, CH_2Cl_2/H_2O, room temp., 30 min, 93%; (c) (i) IBX, EtOAc, reflux, 3 h; (ii) $NaClO_2$, NaH_2PO_4, DMSO, overnight, 80%.

Synthesis of Decarestrictine D through Cross-Metathesis and Yamaguchi Macrolactonization

With substantial amounts of both the fragments in hand, we required to generate the *trans*-olefin and carry out the subsequent reactions to complete the synthesis of target molecule. We then proceeded with the synthesis initially by cross-olefin metathesis (Scheme 5). Thus cross-metathesis of olefin **10** (2 equiv.) and acid **18** (1 equiv.) with Grubbs' second-generation catalyst (20 mol-%) furnished the seco acid **19** in 54% yield with olefin ratio 5:1 in favour of *E*-isomer. The required *trans*-isomer could easily be separated through flash column chromatography.



Scheme 5. Synthesis of decarestrictine D through cross-metathesis and Yamaguchi macrolactonization: (a) $RuCl_2(=CHPh)(PCy_3)$-(IEMS), CH_2Cl_2, room temp., 2 days, 54%; (b) $RuCl_2(=CHPh)$-(PCy_3)(IEMS), CH_2Cl_2, room temp., 2 days, 38%; (c) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 2 h, room temp. then C_6H_6, DMAP, 80 °C, 1 h then reflux, 1 h, 32%; (d) $TiCl_4$, CH_2Cl_2, 0 °C to room temp., 30 min, 78%.

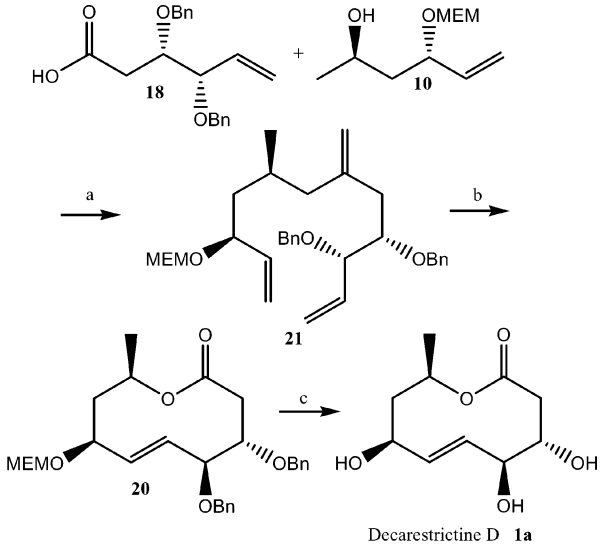
To improve the yield and *E*-selectivity, we further investigated the cross-metathesis reaction with different functionalities in both the fragments. Thus olefin **10** was coupled with olefin **17** (precursor of olefin **18**) in presence of Grubbs' second-generation catalyst to furnish the coupled product **19a** albeit in low yield and poor selectivity. Even the use of TBS, Ac as protecting groups, could not improve the results in terms of yield and selectivity.

With desired *seco*-acid **19** in hand, we turned our attention to get the macrolactone via Yamaguchi macrocyclization. However, macrolactonization of **19** under Yamaguchi conditions[16] provided the macrocyclic lactone **20** in 32% yield only. The low yield obtained could probably be attributed to destabilizing nonbonded, transannular interactions and unfavourable entropic factors.[17] Compound **20** on subsequent cleavage of the protective groups afforded the target molecule **1a** in 78% yield (Scheme 5).

Synthesis of Decarestrictine D through Ring-Closing Metathesis

In order to circumvent the problem of low yield in the cross-metathesis step as well as in macrolactonization, we

thought it appropriate to use Yamaguchi coupling reaction initially for the diene ester formation and then ring-closing metathesis[18] for macrocyclization as the last step in the synthesis (Scheme 6). To this end the alcohol **10** was coupled with acid **18** under Yamaguchi conditions to give the diene **21** in 89% yield. The diene **21** was treated with Grubbs' first generation catalyst to give the α,β-unsaturated lactone in 82% yield with olefin ratio 8:1 in favour of *E*-isomer, which were separable on column chromatography. Global deprotection of **20** using $TiCl_4$ in CH_2Cl_2 gave the target molecule decarestrictine D (**1a**) in 78% yield. $[\alpha]_D^{25}$ = –63.7 (*c* = 0.46, EtOH) [ref.[1b] $[\alpha]_D$ = –62.0 (*c* = 0.4, EtOH)]. The physical and spectroscopic data of **1a** were in full agreement with the literature data.[3] The overall yields and number of steps involved in our synthesis are comparable with those reported in the literature.



Scheme 6. Synthesis of decarestrictine D through ring-closing metathesis: (a) 2,4,6-trichlorobenzoyl chloride, DMAP, Et_3N, THF, 0 °C to room temp., 20 h, 89%; (b) $(PCy_3)_2$ $Ru(Cl)_2$=CH–Ph (20 mol-%), CH_2Cl_2, reflux, 14 h, 82%; (c) $TiCl_4$, CH_2Cl_2, 0 °C to room temp., 30 min, 78%.

Conclusions

In conclusion, a convergent and efficient total synthesis of decarestrictine D, with high enantioselectivities has been accomplished in which all the stereocentres were generated by means of Jacobsen's hydrolytic kinetic resolution and asymmetric dihydroxylation, and lactone moiety was achieved by ring closing metathesis. This approach could be used for synthesis of other isomers of decarestrictine D for structure–activity relationship. Currently work is in progress in this direction.

Experimental Section

General: Solvents were purified and dried by standard procedures before use. Melting points are uncorrected. Optical rotations were measured by using the light of the sodium-D line and a JASCO-181 digital polarimeter. Infrared spectra were recorded on a Perkin–Elmer model 683 grating Infrared spectrometer. ^1H NMR (200 MHz), (500 MHz) and ^{13}C (50 MHz), (125 MHz), NMR spectra were recorded in $CDCl_3$ solution with residual $CHCl_3$ (δ_H = 7.27 ppm) and (δ_C = 77.00 ppm) as internal standard. Mass spectra were obtained with an API Q STARPULSAR spectrometer using electron spray ionization [(ESI), solvent medium: acetonitrile or methanol] technique. Elemental analyses were carried out on a Carlo–Erba CHNS-O analyzer. Petroleum ether of boiling range 60–80 °C was used. Column chromatography were performed on silica gel (60–120 and 100–200 mesh) using a mixture of petroleum ether/ethyl acetate.

(*R*)-Propylene Oxide (2): The racemic propylene oxide was resolved to (*R*)-propylene oxide (**2**) in high enantiomeric excess by the HKR method following a literature procedure.[10a]

For (*R*)-propylene oxide $[\alpha]_D^{25}$ = +11.4 (neat); ref.[10a] $[\alpha]_D^{25}$ = –11.6 (neat) for (*S*)-propylene oxide.

(*R*)-4-Pentene-2-ol: This compound was prepared from (*R*)-propylene oxide according to ref.[8f]

(*R*)-*tert*-Butyldimethyl(pent-4-en-2-yloxy)silane (3): To a stirred soluion of the above-mentioned alcohol (3.0 g, 34.83 mmol) in CH_2Cl_2 (25 mL), imidazole (3.57, 52.24 mmol) was added. To this solution *tert*-butylchlorodimethylsilane (5.77 g, 38.31 mmol) was added at 0 °C and the mixture was stirred at room temperature for 4 h. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2 (3 × 50 mL). The extract was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (49:1) as eluent provided **3** (6.56 g, 94%). $[\alpha]_D^{25}$ = –14.46 (*c* = 1.8 in $CHCl_3$). The spectroscopic data such as ^1H NMR, ^{13}C NMR and IR were in accord with those described in literature.[19]

Ethyl (*R*,*E*)-5-(*tert*-Butyldimethylsilyloxy)hex-2-enoate (4): The olefin **3** (2 g, 9.98 mmol) was diluted with benzene (20 mL) and degassed for 15 minutes. Ethyl acrylate (2.5 g, 24.95 mmol, freshly distilled) was then added to the reaction flask followed by Grubbs' second-generation catalyst (0.169 g, 0.20 mmol). The reaction was allowed to stir for 20 h under argon at room temperature, at which time, it was allowed to oxidize by opening the reaction to air and stirring overnight. The dark brown solution was then concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (19:1) as eluent provided the α,β-unsaturated ester **4** (2.18 g, 80%) as a light yellow colour liquid. $[\alpha]_D^{25}$ = –9.60 (*c* = 1.02 in $CHCl_3$); ref.[20] $[\alpha]_D^{25}$ = –9.5 (*c* = 1 in $CHCl_3$). The spectroscopic data such as ^1H NMR, and ^{13}C NMR were in accord with those described in literature.[20]

Ethyl (2*R*,3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)-2,3-dihydroxyhexanoate (5): To a mixture of $K_3Fe(CN)_6$ (7.25 g, 22.02 mmol), K_2CO_3 (3.04 g, 22.02 mmol) and $(DHQ)_2PHAL$ (57 mg, 1 mol-%), in *t*BuOH/H_2O (1:1, 40 mL) cooled to 0 °C was added OsO_4 (0.29 mL, 0.1 M in toluene, 0.4 mol-%) followed by methanesulfonamide (0.70 g, 7.34 mmol). After stirring for 5 min at 0 °C, the olefin **4** (2.0 g, 7.34 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (11 g). The stirring was continued for 45 min and the solution was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:1) as eluent afforded diol **5** (2.16 g, 96%) in >95% *de* as a colorless syrup. $[\alpha]_D^{25}$ = –10.37 (*c* = 1.26 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 4.27 (q, *J* = 7.2 Hz, 2

H), 4.20–4.05 (m, 2 H), 3.98 (d, J = 6.6 Hz, 1 H), 3.28 (br. s, 1 H), 3.11 (br. s, 1 H), 1.93 (dd, J = 10.8, 1.3 Hz, 1 H), 1.54 (dd, J = 8.2, 6.2 Hz, 1 H), 1.32 (t, J = 7.1 Hz, 3 H), 1.20 (d, J = 6.0 Hz, 3 H), 0.89 (s, 9 H), 0.09 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.2, 74.1, 69.3, 66.4, 61.5, 42.2, 25.6, 23.2, 17.8, 14.0, –4.7, –5.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3439, 3020, 2958, 2931, 2401, 1734, 1656, 1472, 1446, 1257, 1215, 1085, 978 cm^{-1}. $C_{14}H_{30}O_5Si$ (306.47): calcd. C 54.87, H 9.87; found C 54.74, H 9.82. MS (ESI): m/z = 329 [M + Na]$^+$.

Ethyl (4*R*,5*S*)-5-[(*R*)-2-(*tert*-Butyldimethylsilyloxy)propyl]-2,2-dimethyl-1,3-dioxolane-4-carboxylate (6): To a solution of the diol **5** (2.0 g, 6.53 mmol), *p*TSA (50 mg) in CH_2Cl_2 (75 mL) was added 2,2-dimethoxypropane (1.02 g, 1.2 mL, 9.79 mmol) and mixture stirred for 2 h. Solid $NaHCO_3$ was added and stirring continued for 1.5 h. The solution was filtered through a pad of neutral alumina and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave acetonide ester **6** (2.01 g, 89%) as a colorless liquid. $[\alpha]_D^{25}$ = –23.05 (c = 1.40 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.26 (q, J = 8.0 Hz, 2 H), 4.16–4.09 (m, 1 H), 4.07–4.03 (m, 2 H), 1.70–1.61 (m, 2 H), 1.45 (s, 3 H), 1.43 (s, 3 H), 1.29 (t, J = 7.1 Hz, 3 H), 1.19 (d, J = 6.4 Hz, 3 H), 0.89 (s, 9 H), 0.06 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.5, 110.6, 78.9, 75.8, 65.1, 61.0, 43.3, 27.1, 25.6, 24.4, 17.8, 14.0, –4.5, –5.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3021, 2957, 2931, 1751, 1655, 1473, 1375, 1216, 1144, 1084, 952, 839, 758 cm^{-1}. $C_{17}H_{34}O_5Si$ (346.53): calcd. C 58.92, H 9.89; found C 59.01, H 9.86. MS (ESI): m/z = 369 [M + Na]$^+$.

{(4*S*,5*S*)-5-[(*R*)-2-(*tert*-Butyldimethylsilyloxy)propyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methanol (7): To a solution of ester **6** (2 g, 5.77 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was added dropwise DIBAL-H (6.35mL, 6.35 mmol, 1 M in toluene) through a syringe. The reaction mixture was allowed to warm to room temperature over 2 h, then re-cooled to 0 °C and treated with saturated solution of sod./pot. tartrate. The solid material was filtered through a pad of Celite and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (17:3) as eluent gave alcohol **7** (1.65 g, 94%) as a colorless liquid. $[\alpha]_D^{25}$ = –42.51 (c = 1.20 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.05–4.00 (m, 2 H), 3.80–3.70 (m, 1 H), 3.63 (d, J = 4.9 Hz, 2 H), 2.18 (s, 1 H), 1.58 (t, J = 5.7 Hz, 2 H), 1.40 (s, 3 H), 1.38 (s, 3 H), 1.19 (d, J = 6.1 Hz, 3 H), 0.89 (s, 9 H), 0.07 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 108.6, 81.5, 73.7, 65.5, 61.9, 42.7, 27.4, 26.8, 25.8, 24.6, 17.9, –4.5, –5.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3461, 3019, 2957, 2931, 2858, 1719, 1472, 1380, 1256, 1215, 1167, 1047, 952 cm^{-1}. $C_{15}H_{32}O_4Si$ (304.5): calcd. C 59.17, H 10.59; found C 59.23, H 10.57. MS (ESI): m/z = 327 [M + Na]$^+$.

***tert*-Butyl{(*R*)-1-[(4*S*,5*R*)-5-(iodomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]propan-2-yloxy}dimethylsilane (8):** To a stirred solution of alcohol **7** (1.2 g, 3.94 mmol) in CH_2Cl_2 (40 mL) at 0 °C under nitrogen was added triethylamine (1.65 mL, 11.82 mmol) followed by tosyl chloride (0.90 g, 4.73 mmol). After being stirred for 2 h at room temperature, the reaction mixture was diluted with H_2O, and extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with water, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure to give tosyl as a pale yellow oil, which was used as such for the next step, without further purification. Tosyl (1.8 g, 3.92 mmol) was dissolved under argon in dry 2-butanone (20 mL) and was treated with NaI (1.76 g, 11.77 mmol). The reaction mixture was refluxed for 6 h. After cooling to room temperature the volatiles were removed under reduced pressure. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (19:1) as eluent gave iodo compound **8** (1.42 g, 87%) as a colorless liquid. $[\alpha]_D^{25}$ = –38.04 (c = 1.0 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.07–3.88 (m, 2 H), 3.55–3.51 (m, 1 H), 3.31 (d, J = 4.9 Hz, 1 H), 3.25 (d, J = 4.9 Hz, 1 H), 1.57 (t, J = 6.7 Hz, 2 H), 1.43 (s, 3 H), 1.41 (s, 3 H), 1.19 (d, J = 6.2 Hz, 3 H), 0.91 (s, 9 H), 0.08 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 109.5, 81.9, 78.3, 68.7, 37.8, 27.3, 25.6, 25.5, 18.1, 3.8, –3.8, –4.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3020, 2957, 2930, 2857, 2400, 1522, 1472, 1382, 1299, 1215, 1035, 837 cm^{-1}. $C_{15}H_{31}IO_3Si$ (414.39): calcd. C 43.48, H 7.54; found C 43.36, H 7.48.

(3*S*,5*R*)-5-(*tert*-Butyldimethylsilyloxy)hex-1-en-3-ol (9): A mixture of compound **8** (1.4 g, 3.38 mmol) and zinc (0.44 g, 6.76 mmol) in refluxing ethanol (15 mL) under nitrogen was stirred for 8 h. The zinc was filtered and filtrate concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave **9** (0.73 g, 94%) as a light yellow liquid. $[\alpha]_D^{25}$ = –29.18 (c = 1.0 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.03–5.79 (m, 1 H), 5.36–5.06 (m, 2 H), 4.52–4.41 (m, 1 H), 4.24–4.06 (m, 1 H), 2.18 (br. s, 1 H), 1.75–1.62 (m, 2 H), 1.23 (d, J = 6.2 Hz, 3 H), 0.92 (s, 9 H), 0.10 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 141.1, 113.7, 69.6, 66.9, 44.5, 25.7, 23.0, 17.9, –4.5, –5.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3451, 3081, 2955, 2936, 2856, 1642, 1472, 1456, 1384, 1226, 1075, 940 cm^{-1}. $C_{12}H_{26}O_2Si$ (230.42): calcd. C 62.55, H 11.37; found C 62.48, H 11.41. MS (ESI): m/z = 253 [M + Na]$^+$.

(2*R*,4*S*)-4-[(2-Methoxyethoxy)methoxy]hex-5-en-2-ol (10): A mixture of compound **9** (0.5 g, 2.17 mmol), diisopropylethylamine (0.84 g, 1.13 mL, 6.5 mmol), MEM-Cl (0.32 g, 0.30 mL, 2.60 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 8 h. The reaction mixture was quenched with water and extracted with CH_2Cl_2, washed with water, brine, dried (Na_2SO_4) and evaporated to afford crude product, which was used as such for the next step without purification. To a solution of olefin (0.69 g, 2.17 mmol) in THF (10 mL) was added TBAF (3.25 mL, 3.25 mmol, 1.0 M solution in THF) at room temperature. The reaction mixture was stirred for 6 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave alcohol **10** (0.33 g, 75% from both the steps) as a colorless liquid. $[\alpha]_D^{25}$ = –95.88 (c = 1.22 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.80–5.63 (m, 1 H), 5.29–5.15 (m, 2 H), 4.83 (s, 2 H), 4.05–3.90 (m, 1 H), 3.74–3.69 (m, 1 H), 3.60–3.41 (m, 4 H), 3.39 (s, 3 H). 2.39 (br. s, 1 H), 1.71–1.57 (m, 2 H), 1.21 (d, J = 6.2 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 137.7, 116.7, 92.11, 73.9, 71.6, 66.6, 63.1, 58.8, 44.5, 23.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3462, 3016, 2968, 2893, 2448, 1645, 1456, 1422, 1367, 1241, 1216, 1133, 1098, 993 cm^{-1}. $C_{10}H_{20}O_4$ (204.26): calcd. C 58.80, H 9.87; found C 58.64, H 9.81. MS (ESI): m/z = 227 [M + Na]$^+$.

2-[2-(4-Methoxybenzyloxy)ethyl]oxirane (12): To a solution of 3-butene-1-ol (**11**) (5.0 g, 69.34 mmol) in dry THF (50 mL) was added sodium hydride (50%, 5.0 g, 104.00 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly *p*-methoxybenzyl bromide (16.73 g, 83.21 mmol) and tetra-*n*-butylammonium iodide (2.56 g, 6.93 mmol) with further stirring for 2 h at room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with water (3 × 100 mL), brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (8:2) as eluent furnished the mono-PMB-protected olefin (12.40 g,

93%) as a colorless oil. To a stirred solution of olefin (7 g, 36.41 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added *m*CPBA (50%) (15.08 g, 43.69 mmol). The reaction mixture was stirred at room temperature for 8 h and quenched by saturated $NaHCO_3$ solution, extracted with CH_2Cl_2, washed with sat. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (17:3) as eluent afforded the epoxide **12** (7.28 g, 96%) as a colorless liquid. The spectroscopic data such as ^1H NMR, ^{13}C NMR and IR were in accord with those described in literature.[21]

(*E*)-1-[(Hex-3-en-5-ynyloxy)methyl]-4-methoxybenzene (13): A dark brown slurry of lithium acetylide EDA complex (7.74 g, 84.03 mmol) in dry DMSO (10 mL) was stirred with epoxide **12** (7 g, 33.61 mmol) overnight at room temperature. After the reaction mixture was quenched with ice, 0.3 N H_2SO_4 was used to neutralize the resultant basic solution to pH 7, after which the product was extracted with diethyl ether, washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (17:3) as eluent yielded the acetylenic alcohol (7.0 g, 89%) as a light yellow color liquid.

To a stirred solution of acetylenic alcohol (6.5 g, 27.74 mmol) in CH_2Cl_2 (40 mL) at 0 °C under nitrogen was added triethylamine (5.61 g, 7.7 mL, 55.49 mmol) followed by mesyl chloride (3.81 g, 33.29 mmol). After being stirred for 2 h at room temperature, the reaction mixture was diluted with H_2O, and extracted with CH_2Cl_2 (50 mL). The combined organic layers were washed with water, brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was used as such for the next step without further purification.

To a solution of mesylate (7 g, 22.41 mmol) in toluene (50 mL) were added DBU (3.75 g, 3.68 mL, 24.65 mmol). The reaction mixture was heated to reflux for 4 h. The reaction was cooled to room temperature and diluted with water and EtOAc. The two phases were separated and the aqueous phase was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave acetylide olefin **13** (3.97 g, 82%) as a colorless syrup. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.8 Hz, 2 H), 6.87 (d, J = 8.8 Hz, 2 H), 6.27 (dt, J = 7.3, 1.5 Hz, 1 H), 5.60–5.51 (m, 1 H), 4.45 (s, 2 H), 3.82 (s, 3 H), 3.50 (t, J = 6.6 Hz, 2 H), 2.81 (s, 1 H), 2.41 (q, J = 6.7 Hz 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 156.2, 142.9, 130.2, 129.2, 113.7, 110.3, 82.2, 76.1, 72.6, 68.5, 55.2, 33.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3011, 2935, 2862, 2100, 1719, 1612, 1586, 1514, 1465, 1422, 1363, 1249, 1173, 1095, 1035, 822, 757 cm^{-1}. MS (ESI): m/z = 239 $[M + Na]^+$. $C_{14}H_{16}O_2$ (216.28): calcd. C 77.75, H 7.46; found C 77.82, H 7.42.

(3*S*,4*S*)-6-(4-Methoxybenzyloxy)hex-1-yne-3,4-diol (14): To a mixture of $K_3Fe(CN)_6$ (11.42 g, 34.68 mmol), K_2CO_3 (4.79 g, 34.68 mmol) and $(DHQ)_2PHAL$ (90 mg, 1 mol-%), in *t*BuOH/H_2O (1:1, 60 mL) cooled to 0 °C was added OsO_4 (0.46 mL, 0.1 M in toluene, 0.4 mol-%) followed by methane sulfonamide (1.10 g, 11.56 mmol). After stirring for 5 min at 0 °C, the olefin **13** (2.5 g, 11.56 mmol) was added. The reaction mixture was stirred at 0 °C for 24 h and then quenched with solid sodium sulfite (17 g). The stirring was continued for 45 min and the solution was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent gave diol **14** (2.72 g, 94%) in 94% *ee* as a colorless syrup. $[\alpha]_D^{25}$ = +12.77 (c = 0.9 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.23 (d, J = 8.4 Hz, 2 H), 6.86 (d, J = 8.4 Hz, 2 H), 4.46 (s, 2 H), 4.23 (dd, J = 3.7, 2.1 Hz, 1 H), 3.89–3.84 (m, 1 H), 3.80 (s, 3 H), 3.73–3.65 (m, 2 H), 3.09 (br. s, 1 H), 2.88 (br. s, 1 H), 2.47 (s, 1 H), 1.99–1.79 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.3, 129.7, 129.4, 113.9, 82.2, 74.1, 73.8, 72.9, 67.7, 65.8, 55.2, 32.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3307, 3019, 2935, 2400, 1656, 1514, 1367, 1216, 1076, 992, 858 cm^{-1}. MS (ESI): m/z = 273 $[M + Na]^+$. $C_{14}H_{18}O_4$ (250.29): calcd. C 67.18, H 7.25; found C 67.21, H 7.24.

(3*S*,4*S*)-6-(4-Methoxybenzyloxy)hex-1-ene-3,4-diol (15): To a solution of **14** (2.5 g, 9.99 mmol) in 5 mL of ethyl acetate/pyridine/1-octene (10:1:1) was added Lindlar's catalyst (10 mg). The reaction mixture was stirred for 2 h under a balloon of H_2 at room temperature and filtered through a Celite pad. The filtrate was concentrated and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:2) as eluent to give olefin **15** (2.37 g, 94%) as a colorless liquid. $[\alpha]_D^{25}$ = +10.45 (c = 1.0 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.3 Hz, 2 H), 6.89 (d, J = 8.3 Hz, 2 H), 5.94–5.77 (m, 1 H), 5.38–5.19 (m, 2 H), 4.44 (s, 2 H), 3.95 (t, J = 5.7 Hz, 2 H), 3.79 (s, 3 H), 3.69–3.62 (m, 2 H), 2.75 (br. s, 2 H), 1.84–1.76 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.2, 137.40, 129.8, 129.2, 116.9, 113.7, 75.8, 73.0, 72.7, 67.7, 55.1, 32.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3428, 3017, 2957, 2935, 2868, 2401, 1612, 1586, 1513, 1464, 1422, 1249, 1216, 1083, 933, 849 cm^{-1}. MS (ESI): m/z = 275 $[M + Na]^+$. $C_{14}H_{20}O_4$ (252.31): calcd. C 66.65, H 7.99; found C 66.58, H 8.04. ^1H NMR (200 MHz, $CDCl_3$) of **15a**: δ = 7.24 (d, J = 8.2 Hz, 2 H), 6.87 (d, J = 8.2 Hz, 2 H), 4.47 (s, 2 H), 3.82 (s, 3 H), 3.69 (t, J = 5.6 Hz, 2 H), 3.66–3.64 (m, 1 H), 3.35 (dt, J = 4.7, 1.5 Hz, 1 H), 2.72 (br. s, 2 H), 1.89–1.74 (m, 2 H), 1.58–1.44 (m, 2 H), 0.99 (t, J = 7.4 Hz, 3 H) ppm.

1-{[(3S,4S)-3,4-Bis(benzyloxy)hex-5-enyloxy]methyl}-4-methoxybenzene (16): To the above diol **15** (2 g, 7.93 mmol) in DMF (10 mL) at 0 °C was added NaH (60% dispersion in mineral oil, 0.95 g, 23.78 mmol). After 15 min, benzyl bromide (3.25g, 2.3 Ml, 19.02 mmol) was introduced and the reaction mixture further stirred for 4 h at room temperature. Water was carefully added to the reaction mixture, extracted with diethyl ether, washed with water and dried (Na_2SO_4). Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent afforded dibenzyl compound **16** (2.91 g, 85%). $[\alpha]_D^{25}$ = –29.62 (c = 0.7 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.30–7.21 (m, 10 H), 7.13 (d, J = 8.7 Hz, 2 H), 6.79 (d, J = 8.7 Hz, 2 H), 5.84–5.67 (m, 1 H), 5.26–5.17 (m, 2 H), 4.63 (dd, J = 11.4, 8.2 Hz, 2 H), 4.44–4.35 (m, 2 H), 4.29 (s, 2 H), 3.83–3.77 (m, 1 H), 3.71 (s, 3 H), 3.67–3.47 (m, 1 H), 3.45–3.40 (m, 2 H), 1.70–1.56 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.0, 138.8, 138.5, 135.3, 130.5, 129.2, 128.2, 128.1, 127.9, 127.8, 127.6, 127.4, 127.3, 118.6, 113.6, 82.6, 78.1, 73.4, 72.4, 70.4, 66.3, 55.1, 31.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3019, 2933, 2401, 1612, 1513, 1454, 1216, 1153, 1076, 992, 857, 758 cm^{-1}. MS (ESI): m/z = 455 $[M + Na]^+$. $C_{28}H_{32}O_4$ (432.55): calcd. C 77.75, H 7.46; found C 77.82, H 7.45.

(3*S*,4*S*)-3,4-Bis(benzyloxy)hex-5-en-1-ol (17): To a solution of **16** (2.5 g, 5.78 mmol) in CH_2Cl_2 (18 mL) and H_2O (1 mL) at 0 °C was added DDQ (1.57 g, 6.94 mmol) in portions. The resultant mixture was stirred at room temperature for 0.5 h and then saturated aqueous $NaHCO_3$ (10 mL) was added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent afforded alcohol **17** (1.68 g, 93%) as pale yellow oil. $[\alpha]_D^{25}$ = –19.90 (c = 1.38 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.26–7.20 (m, 10 H),

5.86–5.68 (m, 1 H), 5.32–5.23 (m, 2 H), 4.70 (t, J = 11.4 Hz, 1 H), 4.57–4.51 (m, 2 H), 4.38 (d, J = 11.9 Hz, 1 H), 3.93 (t, J = 7.1 Hz, 1 H), 3.61–3.71 (m, 2 H), 1.62–1.41 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.2, 134.8, 128.4, 128.0, 127.9, 127.7, 119.1, 82.2, 78.6. 73.2, 70.6, 60.2, 33.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3377, 3019, 2400, 1654, 1496, 1454, 1215, 1070, 993, 857, 759 cm^{-1}. MS (ESI): m/z = 335 [M + Na]$^+$. $C_{20}H_{24}O_3$ (312.4): calcd. C 76.89, H 7.74; found C 76.84, H 7.78.

(3*S*,4*S*)-3,4-Bis(benzyloxy)hex-5-enoic Acid (18): To a solution of alcohol **17** (1.5 g, 4.80 mmol) in EtOAc (20 mL) was added IBX (4.03g, 14.41 mmol) in one portion and the reaction mixture was refluxed for 3 h. The reaction mixture was filtered through a pad of Celite and filtrate was concentrated to give the crude aldehyde, which was used for the next step without purification.

A solution of 79% $NaClO_2$ (0.651 g, 7.20 mmol) in 1.0 mL of water was added dropwise to a stirred solution of above crude aldehyde (1.49 g, 4.80 mmol) in 0.5 mL of DMSO and NaH_2PO_4 (0.432 g, 3.6 mmol) in 1.0 mL of water in 5 min at room temperature. The mixture was left overnight at room temperature, then 5% aqueous solution of $NaHCO_3$ was added. The aqueous phase was extracted thrice with CH_2Cl_2 and washed with brine, dried (Na_2SO_4), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (4:1) as eluent gave the acid **18** (1.25 g, 80%) as a syrup. $[\alpha]_D^{25}$ = –33.3 (c = 0.7 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 10 H), 5.94–5.76 (m, 1 H), 5.40–5.32 (m, 2 H), 4.76 (d, J = 11.4 Hz, 2 H), 4.67 (d, J = 10.9 Hz, 1 H), 4.44 (d, J = 11.9 Hz, 1 H), 4.11–3.97 (m, 2 H), 2.70 (dd, J = 4.2 Hz, 1 H), 2.52 (dd, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 176.9, 138.1, 134.4, 128.3, 127.9, 127.7, 119.4, 81.01, 77.4, 75.9, 73.5, 36.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3305, 3019, 2976, 2401, 1714, 1520, 1497, 1454, 1423, 1215, 1152, 1072, 993, 933, 854, 757 cm^{-1}. MS (ESI): m/z = 349 [M + Na]$^+$. $C_{20}H_{22}O_4$ (326.39): calcd. C 73.60, H 6.79; found C 73.48, H 6.74.

(3*S*,4*S*,7*S*,9*R*,*E*)-3,4-Bis(benzyloxy)-9-hydroxy-7-[(2-methoxyethoxy)-methoxy]dec-5-enoic Acid (19): The acid **18** (0.100 g, 0.31 mmol) was diluted with CH_2Cl_2 (20 mL) and degassed for fifteen minutes. Alcohol **10** (0.125 g, 0.61 mmol) was then added to the reaction flask followed by Grubbs' second generation catalyst (26 mg, 0.03 mmol). The reaction was allowed to stir for 2 days under argon, at which time, it was allowed to oxidize by opening the reaction to air and stirring overnight. The dark brown solution was then concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent provided the olefin **19** (0.83 g, 54%) as a light yellow color syrup. $[\alpha]_D^{25}$ = –23.05 (c = 1.40 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.26–7.32 (m, 10 H), 5.72 (dd, J = 16.2, 7.1 Hz, 1 H), 5.63 (dd, J = 16.2, 7.1 Hz, 1 H), 4.86 (s, 2 H), 4.67–4.74 (m, 2 H), 4.57–4.63 (m, 2 H), 3.73–3.95 (m, 1 H), 3.60–3.70 (m, 1 H), 3.47–3.55 (m, 2 H), 3.30–3.39 (m, 4 H), 3.25 (s, 3 H), 2.46–2.68 (m, 2 H), 1.65–1.80 (m, 2 H), 1.18 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 177.4, 138.5, 132.2, 129.5, 128.3, 127.9, 127.5, 92.8, 82.1, 74.0, 73.3, 72.5, 71.7, 70.7, 66.2, 62.3, 59.5, 47.0, 36.7, 23.8 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3442, 3038, 2983, 2931, 1720, 1655, 1478, 1362, 1216, 1149, 1084, 956 cm^{-1}. $C_{28}H_{38}O_8$ (502.60): calcd. C 66.91, H 7.62; found C 66.97, H 7.64.

(5*E*,3*S*,4*S*,7*S*,9*R*)-7-[(2-Methoxyethoxy)methoxy]-3,4-bis(benzyloxy)-dec-5-ene-1,9-diol (19a): Prepared by using the similar way as described above for **19**. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.31–7.34 (m, 10 H), 5.70 (dd, J = 15.8, 7.0 Hz, 1 H), 5.64–5.59 (m, 1 H), 4.82 (s, 2 H), 4.74–4.66 (m, 2 H), 4.59–4.52 (m, 2 H), 3.92–3.68 (m, 2 H), 3.62–3.51 (m, 2 H), 3.48–3.39 (m, 2 H), 3.41–3.24 (m, 4 H), 3.23 (s, 3 H), 1.80–1.68 (m, 2 H), 1.65–1.58 (m, 2 H), 1.19 (d, J = 6.6 Hz, 3 H) ppm.

4-[(2-Methoxyethoxy)methoxy]hex-5-en-2-yl 3,4-Bis(benzyloxy)hex-5-enoate (21): To a solution of acid **18** (500 mg, 1.53 mmol) in THF, was added triethylamine (0.32 mL, 2.30 mmol) and 2, 4, 6-trichlorobenzoyl chloride (0.36 mL, 2.30 mmol) under nitrogen atmosphere at 0 °C and the reaction mixture was allowed to stir under this condition for 1 h. To this, alcohol **10** (0.31 g, 1.53 mmol) in THF (5 mL) and catalytic amount of 4-(dimethylamino)pyridine (DMAP) were added successively at 0 °C. Stirring was continued for additional 20 h at room temp. The reaction mixture was quenched with water and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were thoroughly washed with saturated sodium hydrogen carbonate solution, brine, dried (Na_2SO_4), and concentrated to afford the crude product which was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) to afford the ester **21** (0.70 g, 89%) as a colorless syrup. $[\alpha]_D^{25}$ = –41.42 (c = 0.8 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.24–7.29 (m, 10 H), 5.76 (ddd, J = 17.3, 10.0, 7.1 Hz, 1 H), 5.63 (dddd, J = 17.7, 10.0, 7.6, 5.5 Hz, 1 H), 5.35–5.12 (m, 4 H), 4.90 (s, 2 H), 4.74–4.69 (m, 1 H), 4.68–4.63 (m, 1 H), 4.60–4.54 (m, 2 H), 4.09–4.0 (m, 2 H), 3.95–3.89 (m, 2 H), 3.71–3.64 (m, 2 H), 3.51–3.44 (m, 2 H), 3.3 (s, 3 H), 2.67–2.47 (m, 2 H), 1.95–1.70 (m, 2 H), 1.19 (d, J = 6.3 Hz, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.2, 138.5, 138.2, 137.8, 134.6, 129.5, 128.2, 127.5, 119.2, 117.5, 92.8, 81.2, 74.0, 73.3, 72.5, 71.7, 68.1, 67.1, 58.9, 41.9, 36.7, 20.5 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3052, 2961, 2921, 1751, 1655, 1478, 1373, 1216, 1144, 1097, 952, 874, 758 cm^{-1}. MS (ESI): m/z = 535 [M + Na]$^+$. $C_{30}H_{40}O_7$ (512.63): calcd. C 70.29, H 7.86; found C 70.21, H 7.88.

(*E*)-4,5-Bis(benzyloxy)-8-[(2-methoxyethoxy)methoxy]-10-methyl-4,5,9,10-tetrahydro-3*H*-oxecin-2(8*H*)-one (20). i) Yamaguchi Macrolactonization: To a solution of *seco*-acid **19** (0.150 g, 0.30 mmol) in THF (4 mL) were added Et_3N (0.10 mL, 0.75 mmol) and 2,4,6-trichlorobenzoyl chloride (0.182 g, 0.75 mmol) and the reaction mixture was stirred for 2 h at room temperature under argon atmosphere and then diluted with benzene (150 mL). The resulting reaction mixture was added dropwise to a solution of DMAP (0.273 g, 2.24 mmol) in benzene (20 mL) at 80 °C over 1 h and the mixture was stirred for additional 1 h under reflux. The reaction mixture was washed with aq. citric acid solution and brine. The organic layer was dried (Na_2SO_4) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent provided the lactone **20** (0.046 g, 32%) as a light yellow color thick syrup. **ii) RCM:** A mixture of diene **21** (0.2 g, 0.39 mmol) and Grubbs' first-generation catalyst (0.065 g, 0.0078 mmol) in degassed CH_2Cl_2 (50 mL) was stirred under reflux for 14 h. The reaction mixture was evaporated and then purified on silica gel by eluting with petroleum ether/EtOAc (4:1) to afford **20** (0.16 g, 82%) as a thick syrup. $[\alpha]_D^{25}$ = –7.8 (c = 0.43 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.29–7.36 (m, 10 H), 5.72 (dd, J = 15.8, 6.3 Hz, 1 H), 5.67 (dd, J = 15.8, 2.1 Hz, 1 H), 5.19–5.14 (m, 1 H), 4.81 (s, 2 H), 4.65 (d, J = 12.5 Hz, 1 H), 4.54 (d, J = 11.9 Hz, 1 H), 4.48 (d, J = 12.5 Hz, 1 H), 4.47 (d, J = 11.9 Hz, 1 H), 3.92–3.86 (m, 2 H), 3.76–3.73 (m, 2 H), 3.72–3.69 (m, 2 H), 3.57–3.55 (m, 1 H), 3.40 (s, 3 H), 2.64 (dd, J = 15.2, 9.2 Hz, 2 H), 1.81–1.55 (m, 2 H), 1.19 (d, J = 6.4 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.5, 139.5, 132.8, 129.5, 128.3, 127.9, 127.5, 92.8, 81.1, 76.4, 74.1, 73.3, 70.7, 68.1, 60.1, 53.5, 47.4, 42.2, 29.6, 23.7 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3416, 2952, 2931, 1728, 1362, 1236, 1046, 948, 869 cm^{-1}. MS (ESI): m/z = 507 [M + Na]$^+$. $C_{28}H_{36}O_7$ (484.58): C 69.38, H 7.49; found C 69.27, H 7.53.

Decarestrictine D (1a): To a solution of **20** (0.150 g, 0.31 mmol) in anhydrous CH_2Cl_2 (5 mL) under nitrogen at 0 °C was added $TiCl_4$

(0.587 g, 0.34 mL, 3.1 mmol). After 30 min, excess of reagent was quenched with water, extracted with CH_2Cl_2, washed with water, dried (Na_2SO_4), evaporated. The reaction mixture was purified on silica gel by eluting with EtOAc to afford decarestrictine D (**1a**) (52 mg, 78%) as a light yellow color solid. $[\alpha]_D^{25}$ –63.7 (c = 0.46 in $CHCl_3$); ref.[1b] $[\alpha]_D^{20}$ = –62.0 (c = 0.4, in $CHCl_3$); m.p. 116–118 °C (ref.[1b] m.p. 114–115 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.92 (dd, J = 15.9, 7.6 Hz, 1 H), 5.85 (dd, J = 15.9, 2.7 Hz, 1 H), 5.18–5.14 (m, 1 H), 4.77 (br. s, 1 H), 4.43 (dd, J = 3.7, 1.6 Hz, 1 H), 4.21 (m, 1 H), 3.91 (br. s, 1 H), 2.63 (dd, J = 14.4, 1.9 Hz, 1 H) 2.42 (dd, J = 14.4, 6.4 Hz, 1 H), 1.94–1.84 (m, 2 H), 1.55 (br. s, 2 H), 1.23 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.9, 133.7, 129.7, 73.9, 72.5, 72.2, 66.3, 43.1, 33.2, 21.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3422, 2952, 2926, 2845, 1712, 1146, 1042, 969 cm^{-1}. MS (ESI): m/z = 239 [M + Na].

Acknowledgments

P. G. thanks the University Grants Commission (UGC), New Delhi for financial assistance. We are grateful to Dr. Ganesh Pandey for his support and encouragement. Financial support from the Department of Science and Technology (DST), New Delhi (Grant No. SR/S1/OC-40/2003) is gratefully acknowledged.

[1] a) S. Grabley, E. Granzer, K. Hutter, D. Ludwig, M. Mayer, R. Thiericke, G. Till, J. Wink, S. Phillips, A. Zeeck, *J. Antibiot.* **1992**, *45*, 56–65; b) A. Gohrt, A. Zeeck, K. Hutter, R. Kirsch, H. Kluge, R. Thiericke, *J. Antibiot.* **1992**, *45*, 66–73.
[2] W. A. Ayer, M. Sun, L. M. Browne, L. S. Brinen, J. Clardy, *J. Nat. Prod.* **1992**, *55*, 649–653.
[3] M. B. Andrus, T.-L. Shih, *J. Org. Chem.* **1996**, *61*, 8780–8785.
[4] a) R. A. Pilli, M. M. Victor, *Tetrahedron Lett.* **1998**, *39*, 4421–4424; b) R. A. Pilli, M. M. Victor, *J. Braz. Chem. Soc.* **2001**, *12*, 373–385.
[5] a) Y. Kobayashi, M. Asano, S. Yoshida, A. Takeuchi, *Org. Lett.* **2005**, *7*, 1533–1536; b) Y. Kobayashi, S. Yoshida, M. Asano, A. Takeuchi, H. P. Acharya, *J. Org. Chem.* **2007**, *72*, 1707–1716.
[6] P. Radha Krishna, P. V. Narasimha Reddy, *Tetrahedron Lett.* **2006**, *47*, 7473–7476.
[7] S. Colle, C. Taillefumier, Y. Chapleur, R. Liebl, A. Schmidt, *Bioorg. Med. Chem.* **1999**, *7*, 1049–1057.
[8] a) S. V. Kandula, P. Kumar, *Tetrahedron Lett.* **2003**, *44*, 6149–6151; b) P. Gupta, S. V. Naidu, P. Kumar, *Tetrahedron Lett.* **2004**, *45*, 849–851; c) S. V. Naidu, P. Gupta, P. Kumar, *Tetrahedron Lett.* **2005**, *46*, 2129–2131; d) P. Kumar, S. V. Naidu, P. Gupta, *J. Org. Chem.* **2005**, *70*, 2843–2846; e) P. Kumar, S. V. Naidu, *J. Org. Chem.* **2005**, *70*, 4207–4210; f) P. Kumar, P. Gupta, S. V. Naidu, *Chem. Eur. J.* **2006**, *12*, 1397–1402; g) P. Kumar, S. V. Naidu, *J. Org. Chem.* **2006**, *71*, 3935–3941.
[9] a) P. Gupta, R. A. Fernandes, P. Kumar, *Tetrahedron Lett.* **2003**, *44*, 4231–4232; b) S. V. Kandula, P. Kumar, *Tetrahedron Lett.* **2003**, *44*, 1957–1958; c) N. B. Kondekar, S. V. Kandula, P. Kumar, *Tetrahedron Lett.* **2004**, *45*, 5477–5479; d) P. Gupta, S. V. Naidu, P. Kumar, *Tetrahedron Lett.* **2004**, *45*, 9641–9643.
[10] a) S. E. Schaus, B. D. Brandes, J. F. Larrow, M. Tokunaga, K. B. Hansen, A. E. Gould, M. E. Furrow, E. N. Jacobsen, *J. Am. Chem. Soc.* **2002**, *124*, 1307–1315; b) For a review on application of hydrolytic kinetic resolution (HKR) see: P. Kumar, S. V. Naidu, P. Gupta, *Tetrahedron* **2007**, *63*, 2745–2785.
[11] For reviews of alkene cross-metathesis, see: a) S. J. Connon, S. Blechert, *Angew. Chem.* **2003**, *115*, 1944–1967; *Angew. Chem. Int. Ed.* **2003**, *42*, 1900–1923; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4490–4527.
[12] a) H. Becker, K. B. Sharpless, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 448–451; b) H. C. Kolb, M. S. Van Nieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483–2547.
[13] The diastereomeric excess of diol **5** was determined by its ^{1}H and ^{13}C NMR spectroscopic data.
[14] The enantiomeric excess was determined by converting the diol **14** into the Mosher ester and analyzing the ^{19}F spectrum.
[15] K. Ulrike, R. R. Schmidt, *Synthesis* **1985**, 1060–1061.
[16] J. Jnanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
[17] G. Rousseau, *Tetrahedron* **1995**, *51*, 2777–2849.
[18] For reviews on ring-closing metathesis see: a) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450; b) J. Prunet, *Angew. Chem. Int. Ed.* **2003**, *42*, 2826–2830.
[19] A. Kalivretenos, J. K. Stille, L. S. Hegedus, *J. Org. Chem.* **1991**, *56*, 2883–2894.
[20] T. J. Hunter, G. A. O'Doherty, *Org. Lett.* **2002**, *4*, 4447–4450.
[21] J. A. Marshall, G. Schaaf, A. Nolting, *Org. Lett.* **2005**, *7*, 5331–5333.

Received: September 13, 2007
Published Online: January 3, 2008

