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An Efficient and Stereoselective Synthesis of (2R,2'S)-1-O-(2'-hydroxy-hexadecyl)glycerol and Its Oxo Analogs : Potential Antitumour Compounds from Shark Liver Oil.

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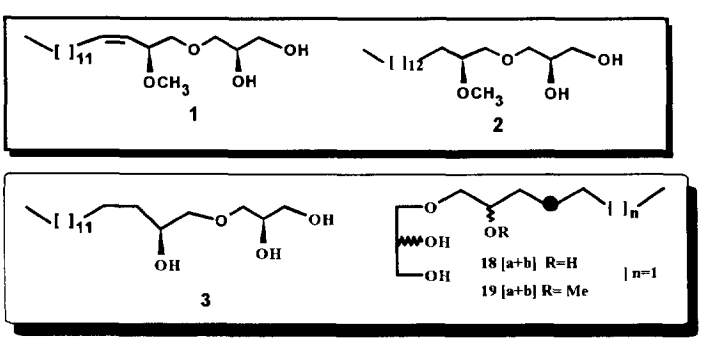
Abstract: Reproducible, high-yielding, cost efficient, regio-and stereoselective synthesis of the title compound **3** isolated from Shark Liver Oil has been described. The compound **3** is prepared in an overall yield of 41% from chiral synthon **4** by the sequential reaction of **4** with C-13 Wittig salt; hydrogenation; epoxidation and regioselective opening. The oxo analogs **18** and **19** are prepared from four different achiral synthons by the sequential regioselective opening of the corresponding epoxide with different alcohols, methylation and deprotection strategies.

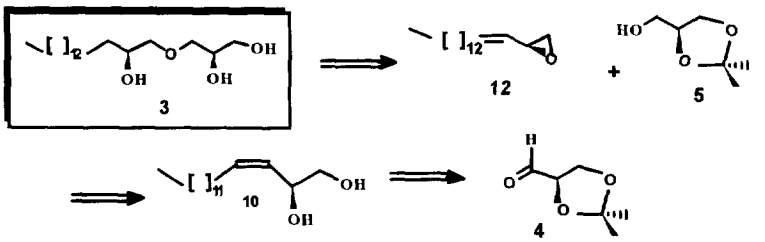
Alkyl glycerol ethers isolated from Greenland shark liver oil[1-3] have been shown to exhibit antibacterial, anticholestermic, antitumour and antimicrobial activities.[4-6] More recently Broult et.al.[7] have also reported the positive effect of alkyl glycerol ethers in the treatment of **AIDS**. Owing to their varied therapeutic applications,[8,9] these class of compounds serve as attractive synthetic targets. It is also worthwhile to note that synthetic routes to these alkyl glycerol ethers are unexplored. In connection with our work on synthesis and bioactivity studies of alkyl glycerol ethers, it was felt pertinent to provide an unambiguous synthetic route for 2-hydroxy-alkyl glycerol ethers.

Our earlier communication[10] reports the synthesis of **1** and **2**. With a view to providing a shorter and more efficient route to this class of compounds, we now report the synthesis of **3** and the oxo analogs **18** and **19** following different synthetic strategies.



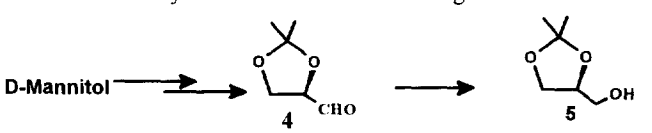
Synthesis of (2R,2'S)-1-O-(2'-hydroxy-hexadecyl)glycerol 3:

The retrosynthetic analysis of compound **3** (retro scheme **1**) reveals that the molecule can be constructed *via* regioselective opening of the chiral epoxide **12** by the chrial alcohol **5**. Further disconnection of **12** provides the chiral diol **10**, which, in turn, can be obtained from the chiral synthon R-isopropylidene glyceraldehyde **4** and C-13 Wittig salt **7**.

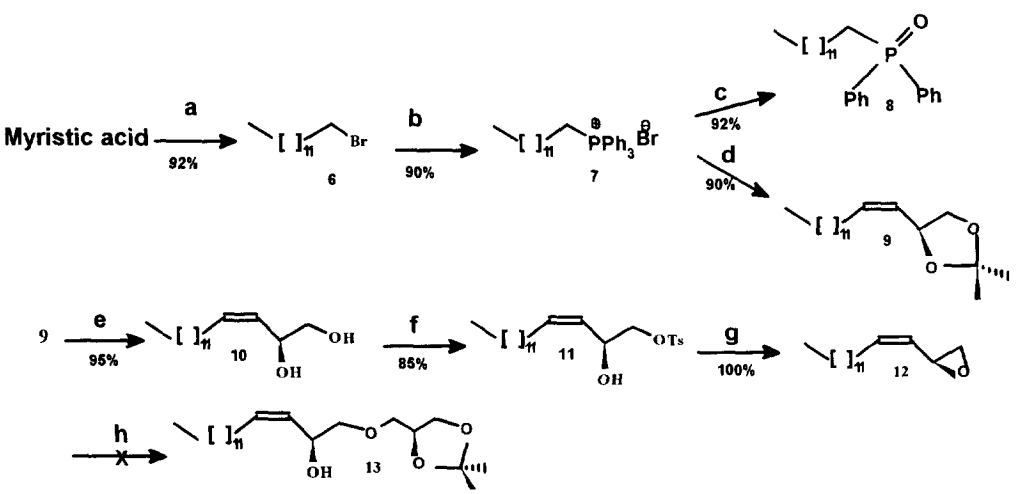


Retro-scheme 1

In the actual synthesis, the chiral diol **10** is obtained from readily available and inexpensive myristic acid (scheme **3**). Myristic acid was converted to the nor-bromo derivative **6** in 92% yield via Hunsdiecker method.[11] The synthesis of the chiral synthon **4** and **5** can be envisaged from D-mannitol (scheme **2**).



Scheme 2



a. Br_2/CCl_4, Red HgO,Reflux,1.5h b. $P(Ph)_3$, CH_3CN, Reflux,24h c. 4, NaH,DMSO,r.t, 6h d. 4,BuLi, THF,-10 °-0°,3h
e. Dowex 50Wx8,MeOH,r.t f. PTsCl, Py,5 °C-0.5h,r.t-18h g. KOH, Benzene, N_2 atm,r.t h. 5, NaH, DMSO, r.t,5 days

Scheme 3

Wittig olefination of aldehyde **4** with the C13-Wittig salt **7** was initially attempted using NaH in DMSO. The product **8** isolated from the reaction exhibited in its ^1H nmr spectrum, a cluster of peaks in the

region between δ 7.4 to 7.8 integrating for ten protons characteristic of aromatic protons and no signals corresponding to olefinic protons. The presence of the C-13 alkyl chain is also indicated by a three proton triplet at δ 0.88 (J=6.57Hz). The ms of **8** revealed a molecular ion peak at m/z 384 and a base peak at m/z 215 corresponding to the fragment $[(C_6H_5)_2\text{-}P(O)\text{-}CH_2]^+$ confirming thereby the formation of tridecyl diphenyl phosphonium oxide.

A plausible mechanism for the formation of **8** has been outlined in Fig **1**. It is pertinent to note that formation of similar products *via* the hydrolysis of phosphonium ylide have been documented in literature.[12]

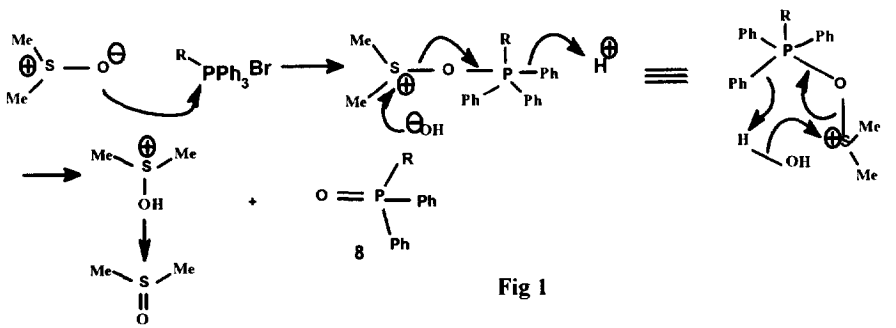


Fig 1

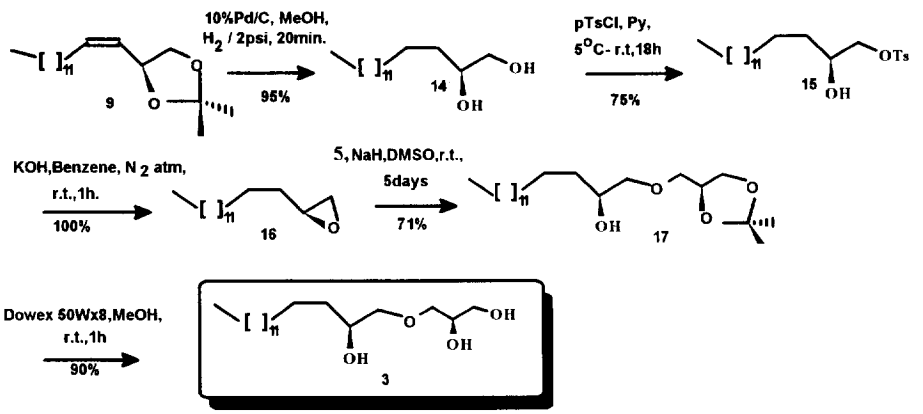
Subsequent attempts of Wittig olefination of **4** was made using n-BuLi in THF. The intermediate **9** formed in 90% yield exhibited IR absorption bands at 3010 and 1660 cm^{-1} characteristic of *cis* olefinic group and 1390 and 1380 cm^{-1} for the isopropylidene group. The ^1H NMR spectrum showed a pair of multiplets at δ 5.63 (tdd, J=7.48,0.92, 10.99 Hz) and 5.39 (tdd, J= 1.52, 8.55, 10.9 Hz) attributable to the *cis* olefinic protons.[13] The formation of a single olefinic *cis* isomer is evident from the ^{13}C NMR spectrum of the compound. In the coupled ^{13}C NMR spectrum, *cis* olefinic and allylic carbons[14] appeared at δc 135.12(d), 127.3(d) and 27.68(t) respectively. The signals at δc 109(s), 26.7(q) and 25.93(q) were characteristic of isopropylidene group and the two signals at δc 72.06(d) and 69.47(t) were assignable to the c-1 and c-2 carbon respectively. The *cis*-isomer **9** is an important precursor of naturally occurring bioactive compounds[15] and is the chiral intermediate for the present synthetic schemes.

Deprotection of the isopropylidene group in **9** was effected with Dowex 50W x8 in methanol to yield (2S,3Z)-hexadec-3-en-1,2-diol (**10**). It was further confirmed by ^{13}C NMR spectrum where the allylic carbon was observed resonating at δc 27.94, a characteristic feature of the *cis* olefin.[14] In the next step compound **10** was monotosylated with p-TsCl in pyridine to yield **11** in 85% which was epoxidized using KOH in dry benzene. The IR spectrum of **12** showed characteristic bands of terminal epoxide and the *cis* olefin at 3010, 1265, 920, and 840 cm^{-1}. The formation of **12** was confirmed by ^1H NMR spectrum where the *cis* olefinic protons were observed at δ 5.73(tdd, J= 0.76, 7.63, 10.99Hz). The three signals, integrating to one proton each at δ 3.62(m), 2.97(dd, J= 5.34, 4.21Hz) and 2.63(dd, J = 2.74, 5.34 Hz), further confirmed the presence of the terminal epoxide. In the ^{13}C NMR spectrum the allylic carbon resonating at δ 27.7 established the formation of the *cis* olefinic group and the two signals at δ 48.52(t) and 48.00(d) corroborated with allylic terminal epoxy group.

Regioselective opening of the chiral epoxide **12** with the alcohol **5** was attempted using NaH in DMSO. However, the desired compound **13** was not isolable even after prolonging reaction time. The failure of the reaction, presumably owing to the presence of the double bond, led us to seek an alternate strategy. The intermediate **9** was hydrogenated using 10% Pd/C to concomitantly effect the removal of the double bond as well as the isopropylidene group. A quantitative yield of the desired product (2S)-hexadecane-1,2-diol **14** was obtained which showed the absence of isopropylidene group and the olefinic double bond in its ^{1}H NMR and IR spectra. Compound **14** is also an analog of **10** which is a useful material in agrochemicals and pharmaceuticals (scheme 3 & 4).[15]

Monotosylate **15** was prepared by reacting **14** with pTsCl in Pyridine at 5°C for 24h in about 75% yield. Formation of **15** was inferred from the IR band at 3560cm^{-1}(OH) and 1800-1600 cm^{-1} (tosyl) and from the ^{1}H NMR signals at δ 7.8, 7.36(Ar), 2.45(Ar-CH_3), 4.04 and 3.88 (Ts-CH_2). It was further established by ^{13}C NMR spectral data. The ditosylated derivative was also isolable in minor amounts.

In order to arrive at the target molecule, **15** was transformed into the corresponding oxirane derivative **16** by treatment with powdered KOH in dry benzene. The IR spectrum exhibited pronounced bands at 920 and 840 cm^{-1} in conjunction with the bands at 1265 and 3030 cm^{-1} suggesting the presence of terminal epoxide group.[16] The formation of the product was further confirmed by ^{1}H NMR spectrum where the methylene protons of the terminal epoxide were observed as doublet of a doublet at δ 2.74 and 2.46 and the methine proton as a multiplet at δ 2.91. The ^{13}C NMR signals at δ 52.25(d) and 47.1(t) were attributed to the carbon bearing terminal epoxy ring. Other signals were commensurate with the structure of **16**. Compound **16** was thus characterised as (2S)-1,2 -epoxy hexadecane with α_D^{26} = -4.49 (scheme 4).



Scheme 4

In the next step **16** was reacted with the chiral alcohol **5** in the presence of NaH in DMSO. The reaction yielded compound **17** resulting from the regioselective opening of the epoxide. The formation of the product was confirmed by the ^{1}H NMR in which the protons of isopropylidene methyls were observed at δ 1.42 and 1.36 and the hydroxy proton appeared as a broad singlet at δ 2.46. In the ^{13}C NMR spectrum also showed the presence of the isopropylidene group at δc 109.46(s), 26.79(q) and 25.35(q). The methine signal at δc 70.31 was attributed to the carbon bearing secondary hydroxy group. The mass spectrum of the

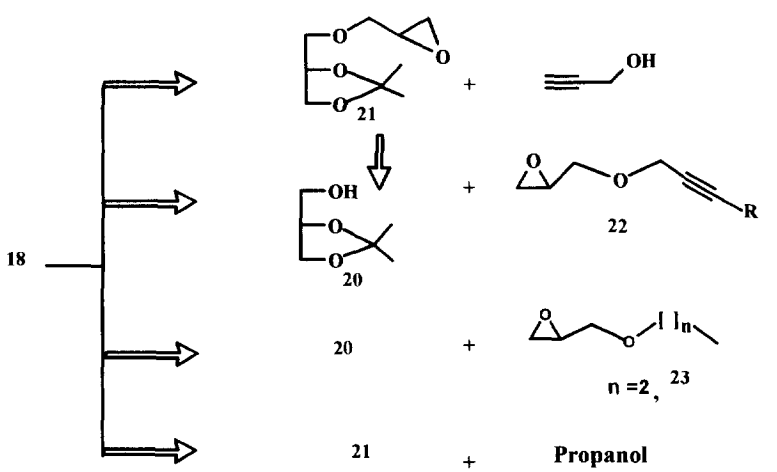
product showed peaks at m/z 357(M^+-CH_3), 339(357-H_2O), 101$(C_5H_9O_2)^+$ and 88$(C_4H_8O_2)$ indicative of presence of isopropylidene group and hydroxy group in the molecule.

Compound **17** was therefore characterised as (2R,2'S)-1-O-(2'-hydroxyhexadecyl)2,3-O-isopropylidene glycerol. In the final step deprotection of the isopropylidene group in **17** was effected with Dowex 50W X8 in methanol. The formation of the product **3** was indicated by the presence of bands at 3450 and 3350 cm^{-1} characteristic of OH in the IR spectrum. It was further confirmed by the ^1H NMR spectrum, which shows the absence of isopropylidene methyls and hence compound **3** was characterized as (2R,2'S)-1-O-(2'-hydroxyhexadecyl)glycerol.

Synthesis of Oxo Analogs, 18 and 19:

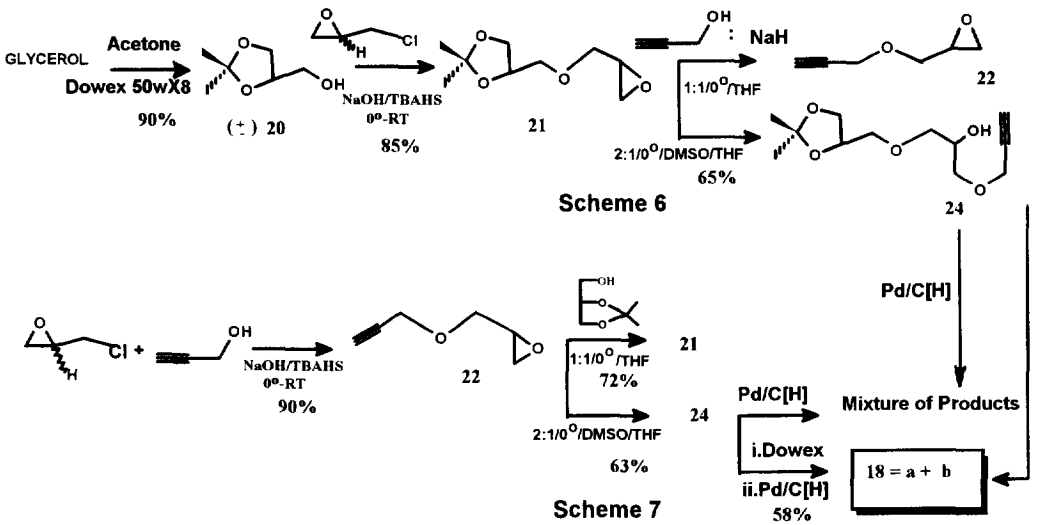
Owing to its interesting biological activity and with a view to study the structure activity relationship,[17a-c] it was felt pertinent to provide an unambiguous synthetic route for oxo analogs of 2-hydroxy- and 2-methoxy- alkyl glycerol ethers. We now report the synthesis of **18** and **19**, the oxo analogs of compound **1**, following different synthetic strategies. Here we present four different routes to the compound **18** starting with the readily available raw materials.

The retrosynthetic analysis of compound **18** (Retro scheme 5) reveals that the molecule can be constructed via four plausible routes. The first two approaches (Scheme 6 and 7) were conceived with a view to elongate the side chain of the target molecule. So the title compound **18** can be constructed via regioselective opening of the stereogenic epoxides **22** or **23** with the achiral alcohol **20** (solketal). The compound **18** can also be constructed by two step process of coupling the epoxides **21** with propanol. In an alternate retrosynthetic analysis, coupling of propargyl alcohol with the racemic epoxide **21** can conveniently be performed furnishing the key intermediate **24**. Further disconnection of **21** provides the alcohol **20**.



Retro-Scheme 5

The epoxide **21** was obtained by the coupling of (±)-solketal **20** with (±)-epichlorohydrin using phase transfer catalyst.[18] Coupling of the propargyl alcohol with the epoxide was initially attempted using NaH in DMSO in the ratio of 1:1(alcohol : NaH). The product **22** (Scheme 6) isolated from the reaction mixture showed peak for the acetylenic proton at δ 2.49ppm as triplet (J=2.38Hz). The absence of the isopropylidene group indicated that it is not the coupled product but a rearranged product. A double doublet at δ 2.64ppm and a multiplet at 3.17ppm denoted the presence of an oxirane ring, which implicitly confirms the formation of the product **22.** The epoxide **22** was intern obtained by the coupling of epichlorohydrin with the propargyl alcohol under PTC condition (Scheme 7). The plausible mechanism for the formation of the epoxide **22** has been outlined in fig 2.



Subsequently, coupling of **21** with propargyl alcohol was successfully performed using 2:1 ratio of alcohol and NaH in DMSO. The intermediate **24** formed in a yield of 65% exhibits IR absorption band at 3300(C≡C-H) and 2100(C≡C) and 1380 & 1390 cm^{-1} for isopropylidene group. The ^1H NMR spectrum showed a triplet at δ 2.46ppm and two singlets at δ 1.36 and 1.42ppm confirming the presence of an acetylenic proton and an isopropylidene group.

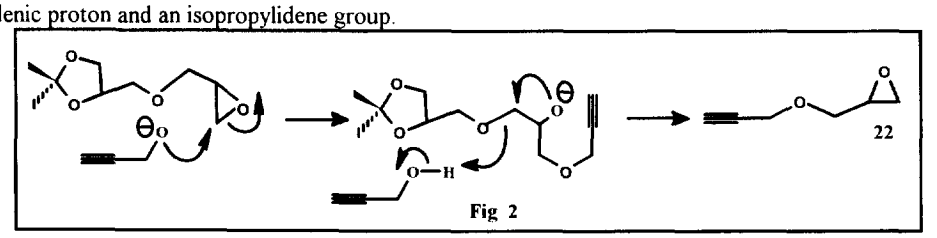
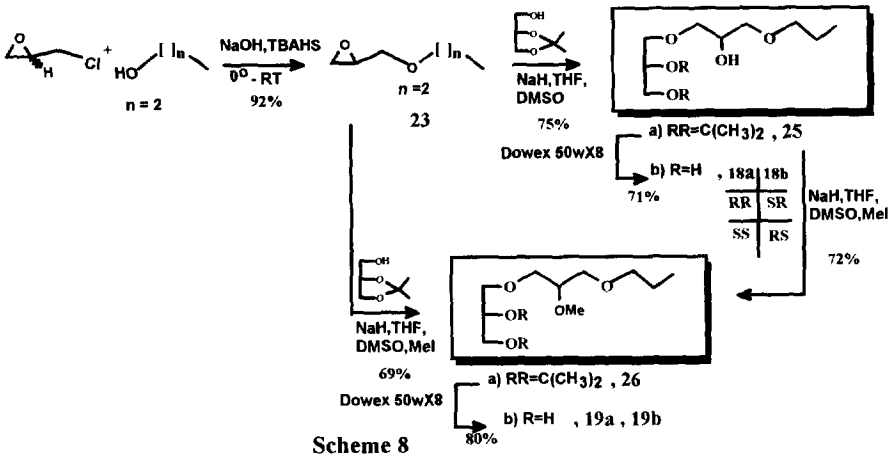


Fig 2

The envisaged strategy required catalytic reduction and demasking of **24.** But catalytic hydrogenation using 10%Pd-C under hydrogen atmosphere provided an intractable mixture of the products. Therefore removal of isopropylidene group prior to the hydrogenation of triple bond was attempted and the desired deprotection was done using Dowex x 50W. The diol thus obtained was subjected to catalytic hydrogenation to provide the diastereomers **18a** and **18b** in an overall yield of 38%. Presence of broad band at 3450cm^{-1} and a three proton triplet at δ 0.98ppm indicated the formation of the product. Similar

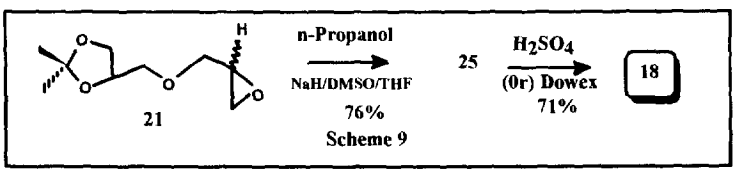
type of reaction scheme was followed for epoxide **22** (scheme 7). But in this case, the yield was lowered to 33%.

In order to reduce the number of steps, we had chosen an alternate strategy. In this method the title compounds **18** and **19** were synthesised in four steps with an overall yield of 49% and 51% respectively (Scheme 8).



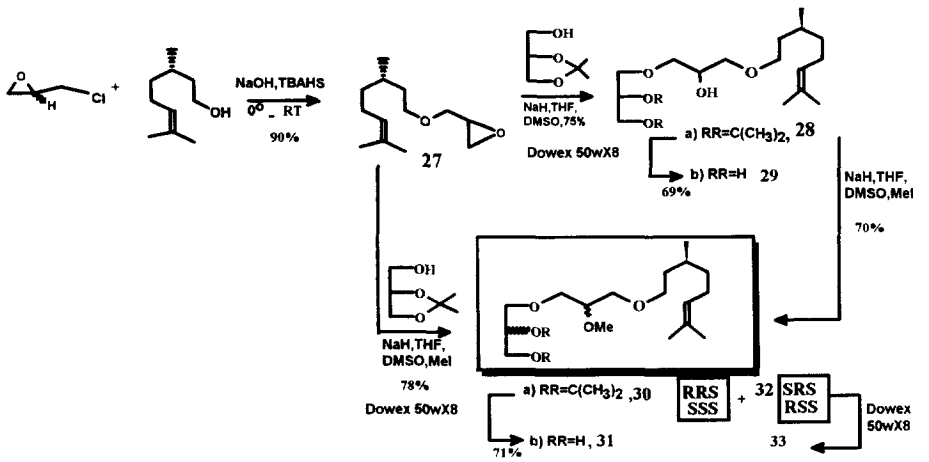
Scheme 8

The epoxide **23** was, therefore, coupled with the solketal using NaH in DMSO to provide the product **25** which was methylated to give **26.** Compound **26** was also obtained by coupling **23** with solketal using NaH followed by *in situ* addition of methyl iodide at 0°C. The methylated product **26** was deprotected using Dowex resin to provide the oxo analog **19.** The presence of two three proton singlets at δ 3.39 and 3.47ppm indicated the formation of diastereomeric mixture of **19**. Similarly coupling of **21** with propanol yielded **18** in an overall yield of 41% (Scheme 9).



Scheme 9

Besides the target molecules, isoprenoid analogs **31** and **33** were also synthesised using cheaply available terpenoid, (S)-citronellol (Scheme 10). The epoxide **27** was subjected to undergo coupling reaction with solketal and *in situ* addition of the methyl iodide provided the diastereomers **30** and **32** in the ratio of 1:1 (by **nmr** integration of -OMe signals).



Scheme 10

The product was subjected to Dowex treatment for the cleavage of isopropylidene group to provide the compounds **31** and **33.** The side chain may be transformed to the oxo analogs of the higher homologs of natural products by reductive ozonolysis followed by Wittig olefination.

In summary, a simple, novel and efficient methodology described herein conveniently affords the title compound **3** in an overall yield of 41% from the chiral synthon **4** and the title compounds **18** and **19** in an overall yield of 49% and 51% respectively from the achiral synthon **23**. This synthetic sequence allows the setereoselective synthesis of **3** for which todate hardly any adequate synthesis are available. The key step in this sequence involves the regio and stereoselective opening of oxirane ring system by the chiral synthon **5**. This methodology is cost-efficient and clearly applicable in the synthesis of diverse range of naturally occurring alkyl glycerol ethers.

Experimental:

Myristic acid, D-mannitol and glycerol were purchased from Aldrich Chemical Co., Dowex 50W X8 resin was purchased from Sigma Chemical Co. and Triphenylphosphine, 10% Pd/C catalyst and sodium hydride were purchased from Fluka Chemical Co. Melting points are reported uncorrected. Laboratory solvents were purified and predried before use according to standard procedures. Petroleum ether of b.p. 60-80°C was used for column chromatography. Temperature is expressed in degree Celsius. IR spectra were recorded on Perkin Elmer 688 Spectrometer. NMR spectra were recorded either on Varian VXR 300S or Varian FT 60A or Varian 100 spectrometer using $CDCl_3$ as the solvent or $CDCl_3$ /CD_3OD(9:1) solution containing TMS as an internal standard with chemical shifts (δ) expressed on ppm down field with respect to TMS. Mass spectra were obtained on CEC-21-110B double focusing mass spectrometer operating at 70eV using direct inlet system. The optical rotations were measured with Shimadzu digital polarimeter. Purity was checked on Shimadzu GC-14A chromatogram.

For all new compounds satisfactory microanalysis obtained: C ± 0.43, H ± 0.52.

Tridecyl diphenyl phosphonium bromide (7)

To a solution of 1-bromotridecane **6**(10g, 0.038mmol) in dry acetonitrile (280ml), triphenyl phosphine (12g, 0.046mmol) was added and the mixture was refluxed for 24h. Reaction was monitored on TLC (25%benzene in petroleum ether). Following the disappearance of the bromo compound on TLC, the solvent was distilled off and the resulting solid was washed with dry ether (50ml x 3) to obtain compound 7 in the form of white solid. Dry weight 18g (90%).

^{1}H NMR ($CDCl_3$,300 MHz) δ : 7.88 to 7.7 (m, 15H, $(C_6H_5)_3$, 3.75 (m, 2H, 1-H_2), 1.66 (brs, 4H, 2-H_2 and 3-H_2), 1.2 (d, 18H, 4-H_2 to 12-H_2) and 0.87 (t, J = 6.56 Hz, 3H, 13-H_3).

Wittig reaction of 2,3-isopropylidene-D-glyceraldehyde 4 with compound 7 in DMSO-NaH

Sodium hydride (288mg of 50% in petroleum wax, 6mmol) was taken in a three necked round bottom flask connected with a reflux condenser and N_2 inlet. It was washed with dry hexane (2 x 5ml). Dimethyl sulfoxide (5ml) was added and the mixture was heated between 60-70^{o}C for 30 min. to form dimsyl sodium (light green colour). The solution was allowed to attain room temperature and compound 7(3g, 5.7mmol) in THF (10ml) was added dropwise over 30 min. The reaction was kept stirring for an additional 1h. (2R)-2,3- isopropylidene glyceraldehyde **4** (1.32g, 10mmol) was then added under N_2 atmosphere and stirred further for 3h at room temperature. After usual workup and column chromatographic purification on silica gel using 20% EtOAc/pet.ether as eluant, a white solid of tridecyl diphenyl phosphonium oxide **8** was obtained in an yield of 2g (92%).

Tridecyl biphenyl phosphonium oxide (8)

m.p 64^{o}C; ν_{max} (film)/cm^{-1} :3060, 3000, 2950, 2850, 1800-1600(Ar), 1460, 1450, 1380, 1220, 1100, 860, 740, and 720; ^{1}H NMR ($CDCl_3$, 300 MHz) δ : 7.8 to 7.4 (m, 10 H, $(C_6H_5)_2$), 2.24 (m, 2H. 1-H_2), 1.65-1.57 (m, 2H, 2-H_2), 1.38 (m, 2H, 3-H_2), 1.22 (d, 18H, 4H to 12-H_2) and 0.88 (t, J = 6.57 Hz, 3H, 13-H_3); ^{13}C NMR ($CDCl_3$,75 MHz) δ : 133.87(s), 132.58(s), 131.4(d), 130.67(d), 130.55 (d), 128.9(d), 128.35(d), 31.7 (t), 30.89(t), 30.71(t), 29.44(t), 29.17(t), 22.51(t), 21.29(t) and 13.92 (q); MS : m/z 384 (M+), 369 (M^+-CH_3), 355 (M+-C_2H_5, 341(M^+-C_3H_7) 327 (M^+-C_4H_9), 313 (M^+-$C5H_{11}$), 299 (M^+-C_6H_{13}), 285(M^+-C_7H_{15}), 271 (M^+-C_8H_{17}), 257 (M^+-C_9H_{19}), 243 (M^+-$C_{10}H_{21}$), 229 (M^+-$C_{12}H_{25}$) and 215 ($C_{13}H_{12}OP$, Base peak).

Wittig reaction of 2,3-isopropylidene D-glyceraldehyde 4 with compound 7 in THF n-butyl lithium

To a cold suspension of compound 7(9.5g, 18mmol) in dry THF (100ml), n-butyl lithium (15%in hexane 12.6ml, 18mol) was added. After the reaction mixture was kept stirring for an hour at 0^{o}C, 2,3-isopropylidene D-glyceraldehyde **4** (5g, 38.4mmol) was added. The orange colour of the solution disappeared gradually. The reaction mixture was then left stirring for an hour during which it attained room temperature. It was then quenched with water, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The semi solid was dissolved in petroleum ether:ether (1:1) mixture and filtered through celite. The filtrate was concentrated under *vacuo* followed by column chromatography on silica gel using 1.5% EtOAc/petroleum ether solvent system as eluant to give an yellow oil of (2S,3Z)-hexadec-3-ene-1,2-diol acetonide **9** (4.5g, 90%).

$[\alpha]_D^{26}$= + 5.06 (c= 3.75,$CHCl_3$);

ν_{max} (film)/cm^{-1} : 3010, 1660 (C=C), 1390, 1380(<$C(CH_3)_2$) 1260, 1220, 1080, 860, 790, 740 and 720 ; ^1H NMR ($CDCl_3$, 300 MHz) δ : 5.63 (tdd, J = 7.48, 0.92, 10.99 Hz, 1H, 4-H), 5.39 (tdd, J = 1.52, 8.55, 10.9 Hz, 1H, 3-H), 4.84 (m, 1H, 2-H), 4.05(dd, J = 6.1, 8.01 Hz, 1H, 1-H_2), 3.51 (dd, J = 7.93, 8.01 Hz, 1H, 1-H_2), 2.1(m, 2H, 5-H_2), 1.42(s, 3H, >$C(CH_3)_2$), 1.39 (s, 3H, >$C(CH_3)_2$), 1.26 (s, 20H, 6-H_2 to 15-H_2) and 0.88 (t, J = 6.56 Hz, 3H, 16-H_3);
^{13}C NMR ($CDCl_3$, 75 MHz) δ : 135.12 (d, C-3), 127.30(d, C-4), 109.00 (s,> $C(CH_3)_2$), 72.06 (d, C-2), 69.47 (t, C-1), 31.88 (t, C-14), 29.59 (t, C-7 to C-11 and C-13), 29.41 (t, C-6), 29.29 (C-12), 27.68 (t, C-5), 26.7 (q, >$C(CH_3)_2$), 25.93 (q, >$C(CH_3)_2$), 22.64 (t, C-15) and 14.00 (q, C-16). MS : m/z 282 (M^+-15).

(2S,3Z)-Hexadec-3-en-1,2-diol (10)

A mixture of (2S,3Z)-hexadec-3-en-1,2-diol acetonide **9** (2g, 6.75mmol) and Dowex 50W X8 (1.5g) resin in methanol (50ml) was stirred at room temperature for four hours. After usual work up the semi solid thus obtained was chromatographed over silica gel (200-400mesh) using ethyl acetate-petroleum ether (1:3) mixture to elute compound **10** (1.6 g, 95%). The purity of the compound was checked by GC (99%).
$[\alpha]_D^{27}$ = +3.84 (c = 12.5 $CHCl_3$);
ν_{max} (film)/cm^{-1}:3480 (OH), 3020, 1660 (C=C), 860 and 720;
^1H NMR ($CDCl_3$, 300 MHz) δ : 5.57 (td, J = 7.48 Hz, 10.99 Hz, 1H, 4-H), 5.35 (dd, J = 8.64, 10.99 Hz, 1H, 3-H), 4.55 (m, 1H, 2-H), 3.66 to 3.44 (m, 2H, 1-H2), 2.85 (brs, 2H, 1-OH and 2-OH), 2.1 (m, 2H, 5-H_2), 1.26 (s, 20H, 6-H to 15-H_2) and 0.88 (t, J = 6.56 Hz, 3H, 16-H_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ : 134.41 (d, C-3), 127.89 (d, C-4), 68.77 (d, C-2), 66.35 (t, C-1), 31.88 (t, C-14), 29.64 (t, C-7 to C-11 and C-13), 29.35 (t, C-6 and C-12), 27.94 (t, C-5), 22.64 (t, C-15) and 14.05 (q, C-16); MS : m/z 225 (M^+-31).

(2S,3Z)-Hexadec-3-en-1,2-diol-1-tosylate (11)

A solution of (2S,3Z)-hexadec-3-en-1,2-diol **10** (1.5g, 5.85mmol) in dry pyridine (25ml) was stirred and cooled to 5°C. Freshly recrystallized p-toluenesulfonyl chloride (1.34g, 7mmol) was added over a period of three hours and the mixture stirred for 18h at room temperature. After usual workup, solvent was evaporated under reduced pressure followed by flash column chromatography using ethyl acetate/petroleum ether (1.5% EtOAc/petroleum ether) as eluants to give compound **11**. Yield : 2g (85%).
$[\alpha]_D^{31}$ = +49.9 (c = 5.5, $CHCl_3$); ν_{max} (film)/cm^{-1} 3500 (OH), 3020, 1800-1600 (Ar), 1600, 980, 860, 720 and 680; ^1H NMR ($CDCl_3$, 60 MHz) δ : 7.6-7.4 (m, 2H, Ar), 7.2-6.9 (m, 2H, Ar), 5.5-4.7 (m, 2H, 3-H and 4-H), 4.6-4.1 (m, 1H, 2-H), 3.8-3.5 (m, 2H, 1-H_2), 2.14 (s, 3H, Ar-CH_3), 1.8 (m, 2H, 5-H_2), 1.26 (s, 20H, 6-H_2 to 15-H_2) and 0.88 (t, 3H, 16-H_3);
^{13}C NMR ($CDCl_3$, 75 MHz) δ : 144.86 (s, C-1 of Ar), 136.65 (d, C-3), 132.53 (s, C-4 of Ar), 129.00 (d, C-2 and C-6 of Ar), 126.82 (d, C-3 and C-5 of Ar), 126.74 (d, C-4), 73.05 (t, C-1), 66.01 (d, C-2), 31.88 (t, C-14), 29.64 (t, C-7 to C-11 and C-13), 29.35 (t, C-6 and C-12), 27.94 (t, C-5), 22.61 (t, C-15), 20.7 (q, Ar-CH_3) and 14.05 (q, C-16); MS : m/z 420 (M^+), 91 (CH_3-C_6H_4, 100%).

(2S,3Z)-1,2-epoxyhexadec-3-ene (12)

To a solution of monotosyl compound **11** (2g, 4.88mmol) in benzene (50 ml), powdered KOH (12 eq) was added and stirred under nitrogen atmosphere for 45 min. till the starting material was not detectable on TLC (20% EtOAc/petroleum ether). The reaction was then filtered through G-4 sintered crucible. The residue was washed with dry benzene and solvent was removed from the combined filtrates under reduced pressure to give compound **12**. Yield : 1.15g (100%).

$[\alpha]_D^{26}$ =-11.59 (c = 25%, $CHCl_3$);

ν_{max} (film)/cm^{-1} 3030, 3010, 2960, 2850, 1660, 1460, 1390, 1265, 1140, 920, 840, 820 and 720;

^1H NMR ($CDCl_3$, 300 MHz) δ : 5.73(dtd, J = 0.76, 7.63, 10.99 Hz, 1H, 3-H), 5.03-4.96 (tdd, J = 1.53, 9.00, 10.99 Hz, 1H, 4-H), 3.62 (m, 1h, 2-H), 2.97 (dd, J = 5.34, 4.21 Hz 1H, 1-H_2), 2.63 (dd, J = 2.74, 5.34 Hz, 1H, 1-H_2), 2.20 (m, 2H, 5-H_2), 1.41 (m, 2H, 6-H_2), 1.26 (s, 18H, 7-H to 15-H_2) and 0.88 (t, J = 6.56 Hz, 16-H_3); ^{13}C NMR ($CDCl_3$,75 MHz) δ : 137.05 (d, C-3), 126.99 (d. C-4), 48.52 (d, C-1), 48.00 (d, C-2), 31.87 (t, C-14), 29.6 (t, C-7 to C-11 and C-13), 29.3 (t, C-12), 29.14 (t, C-6), 27.7(t, C-5), 22.63 (t, C-15) and 14.02 (q, C-16).MS : m/z 238 (M^+).

(2S)-Hexadecan-1,2-diol (14)

To a solution of (2S,3Z)-hexadec-3-en-1,2-diol acetonide **9** (1g, 3.37mmol) in methanol (30 ml), 10% Pd/C (50mg) was added and stirred vigorously under 2psi pressure of H_2 for 20 min. The reaction mixture was filtered through G-4 sintered crucible and the filtrate was concentrated under *vacuo* to give compound **14** (0.82g, 95%). The compound was further purified by crystallization from $CHCl_3$:petroleum ether, 8:2.

$[\alpha]_D^{31}$ =-2.49 (c = 2, $CHCl_3$). ν_{max} (film)/cm^{-1} 3500 (br OH), 1460, 1380, 880 and 720 ;

^1H NMR ($CDCl_3$,CD_3OD , 60 MHz) δ : 3.8-3.3 (m, 5H, 1-H_2 , 2-H, 1-OH and 2-OH), 2.3 (m, 2H, 3-H_2), 1.6 (m, 2H, 4-H_2), 1.26 (s, 22H, 5-H_2 to 15-H_2) and 0.86 (t, 3H, 16-H_3);

^{13}C NMR ($CDCl_3$, CD_3OD, 75 MHz) δ : 71.88 (d, C-1), 66.11 (t, C-1), 32.77 (t, C-3), 31.56 (t, C-14), 29.32 (t, C-5 to C-11 and C-13), 28.99 (t, C-12), 25.26 (t, C-4), 22.29 (t, C-15) and 13.56 (q, C-16) ; MS : m/z 211 (M^+- 31).

(2S)-Hexadecan-1,2-diol-1-tosylate (15)

A solution of (2S)-hexadecan-1,2-diol **14**(500mg,1.94mmol) in dry pyridine (10ml) was stirred and cooled to 5°C. To this cold solution a freshly prepared solution of *p*-toluenesulfonyl chloride (1.1 eq) was added over a period of three hours and stirred further for 18h at room temperature. After usual workup the solvent was evaporated under reduced pressure followed by flash column chromatography using 1%EtOAc/petroleum ether as an eluant to yield compound **15**. Yield: 600 mg (75%).

$[\alpha]_D^{30}$ = + 5.58(c = 2.33, $CHCl_3$); ν_{max} (film)/cm^{-1} : 3560(OH),1800-1600(tosyl), 1460, 1380, 1220, 1200, 1110 and 720; ^1H NMR ($CDCl_3$, 300 MHz) δ : 7.8 (d, J = 8.39 Hz, 2H, 2-H and 6-H of Ar), 7.36 (d, J = 8.69 Hz, 2H, 3-H and 5-H of Ar), 4.04 (dd, J = 2.59, 9.46 Hz, 1H, 1-H2), 3.88 (dd, J = 7.02, 9.45 Hz, 1H, 1-H_2), 3.8 (m, 1H, 2-H), 2.45 (s, 3H, Ar-CH_3), 2.18 (brs, 1H, 2-OH), 1.4 (m, 2H, 3-H_2), 1.25 (s, 24H, 4-H to 15-H_2) and 0.88 (t, J = 6.86 Hz, 3H, 16-H_3);

^{13}C NMR ($CDCl_3$, 75 MHz) δ : 145.00(s, C-2 of Ar), 132.65 (s, C-4 of Ar), 129.9 (d, C-2 and C-6 of Ar), 127.9 (d, C-3 and C-5 of Ar), 73.95 (t, C-1), 69.45 (d, C-2), 32.62 (t, C-3), 31.89 (t, C-14), 29.32 (t, C-5 to C-11 and C-13), 28.99 (t, C-12), 25.26 (t, C-4), 22.29 (t, C-15) and 13.57 (q, C-16);

MS : m/z 412 (M^+), 91 (CH_3-C_6H_4, 100%).

(2S)-1,2-epoxyhexadecane (16)

Powdered KOH(1.2eq) was added to a solution of compound **15**(0.8 g, 1.94 mmol) in dry benzene (20ml) under N_2 atmosphere and stirred for 1h till the starting material disappeared on TLC(15% EtOAc/petroleum ether). The reaction mixture was filtered and washed the residue with dry benzene. The combined organic solution was concentrated under reduced pressure to yield compound **16** (440mg, 95%).
$[\alpha]_D^{26}$ =-4.49 (c =2, $CHCl_3$); ν_{max} (film)/cm^{-1} 3030, 1265, 920, 840 (terminal epoxide) and 720; ^1H NMR ($CDCl_3$, 300 MHz) δ : 2.91 (m, 1H, 2-H), 2.74 (dd, J = 3.96, 5.04 Hz, 1H, 2-H_2), 2.46 (dd, J = 5.04, 2.74 Hz, 1H, 1-H_2), 1.51 (m, 2H, 3-H_2), 1.26 (s, 24H, 4-H_2 to 15-H_2), and 0.88 (t, J = 6.86 Hz, 3H, 16-H_3);
^{13}C NMR ($CDCl_3$, 75 MHz) δ : 52.25 (d, C-2), 47.1 (t, C-1), 32.47 (t, C-3), 31.89 (t, C-14), 29.64 (t, C-6 to C-11 and C-13), 29.43 (t, C-5), 29.32 (t, C-12), 25.94 (t, C-4), 22.65 (t, C-15) and 14.06 (t, C-16); MS : m/z 240 (M^+).

(2S,2'S)-1'-O-(2'-hydroxyhexadecyl)-2,3-O-isopropylidene glycerol (17)

A solution of (2S)-1,2-isopropylidene glycerol **5** (116mg, 0.88mmol) in DMSO (10ml) was added to sodium hydride (4.5mg of NaH 50% in petroleum wax, 0.987mmol) which was washed with dry hexane (2 x 5ml) to remove the wax coating. The mixture was stirred for a period of one hour at room temperature. Epoxide **16** (150mg, 0.63mmol) in DMSO (10ml) was added and the reaction mixture stirred at room temperature for a period of 5 days. The reaction was stopped as soon as the epoxide **16** disappeared on TLC (4% EtOAc/petroleum ether). The reaction mixture was next quenched with cold water, extracted with ether, washed with brine, dried over anhydrous Na_2SO_4 and solvent removed on rotary evaporator. The compound was purified by column chromatography using $CHCl_3$ and $CHCl_3$:MeOH mixture (99:1) as eluants to yield compound **17**. Yield : 160mg (74%).
$[\alpha]_D^{29}$ =+7.59 (c= 2.5, $CHCl_3$); ν_{max} (film)/cm^{-1} 3450 (OH), 1390, 1380[$C(CH_3)_2$], 1220, 1110 (br), 860 and 740; ^1H NMR ($CDCl_3$, 300 MHz) δ : 4.29 (ddt, J = 6.41, 6.25, 5.34 Hz, 1H, 2-H), 4.06 (dd, J = 8.24, 6.41 Hz, 1H, 3-H_2), 3.8 (m, 1H, 2'-H), 3.74 (dd, J = 6.25, 8.24 Hz, 1H, 3-H_2), 3.56 (d, J = 5.34 Hz, 2H, 1-H_2), 3.53 (dd, J = 9.77, 2.98 Hz, 1H, 1'-H_2), 3.34 (dd, J = 8.2, 9.7 Hz, 1H, 1'-H_2), 2.46 (brs, 1H, 2'-OH), 1.45-1.35 (m, 2H, 3'-H_2). 1.42 (s, 3H, >$C(CH_3)_2$). 1.36 (s, 3H, >$C(CH_3)_2$), 1.25 (s, 24H, 4'-H_2 to 15'-H_2) and 0.88 (t, 3H, 16'-H_3);
^{13}C NMR ($CDCl_3$, 75 MHz) δ : 109.46 (s, >$\underline{C}(CH_3)_2$), 76.1 (t, C-1'), 74.72 (d, C-2), 72.25 (t, C-1), 70.31(d, C-2'), 66.58 (t, C-3), 33.05 (t, C-3'), 31.89 (t, C-14'), 29.64 (t, C-5') to C-11' and C-13'), 29.32 (t, C-12'), 26.79(>$C(\underline{C}H_3)_2$), 25.35(t, C-4'), 25.35 (>$C(\underline{C}H_3)_2$), 22.65 (t, C-15') and 14.06 (q, C-16').3.33 & 3.34); MS : m/z 357 (M^+-CH_3), 339 (357 - H_2O), 101 $(C_5H_9O_2)^+$ and 88 $(C_4H_8O_2)^+$.

(2R,2'S)-1'-O-(2'-hydroxyhexadecyl)glycerol (3)

To a solution of compound **17** (100mg,0.27mmol) in methanol (10ml), Dowex 50W X8 (50mg) was added and the mixture stirred at room temperature for one hour. The resultant mixture was filtered through G-4 sintered crucible and concentrated to yield the semi solid compound **3**, yield 85mg (95%). It was

purified by column chromatography, elution was done with $CHCl_3$:MeOH (9:1) to yield the pure compound **3**. Yield 80.5mg (90%).

$[\alpha]_D^{28}$ =+1.49 (c =2, $CHCl_3$:MeOH, 1:1);

ν_{max} (film)/cm^{-1}:3450 (CH-OH), 3350 (CH_2-OH), 1460, 1380, 1160, 1110, 860, 820 and 720;

^1H NMR ($CDCl_3$:MeOH, 95:5, 300 MHz) δ : 3.86 (m, 1H, 2-H), 3.76 (m, 1H, 2'-H), 3.7 to 3.26 (m, 6H, 1-H2, 3-H_2, 1'-H_2), 2.66-2.4 (brs, 5H, 3'-H_2, 1-OH, 2-OH, 2'-OH), 1.4 (m, 2H, 4-H_2), 1.26 (s, 22H, 5-H_2 to 15-H_2), 1.4 (m, 2H, 4-H_2), 1.26 (s, 22H, 5-H_2 to 15-H_2) and 0.88 (t, J = 6.86 Hz, 3H, 16-H_3);

^{13}C NMR ($CDCl_3$:MeOH, 95:5, 75 MHz) δ : 75.79 (t, C-1'), 72.48 (t, C-1), 70.75 (d, C-2), 70.19 (d, C-2'), 63.8 (t, C-3), 32.92 (t, C-3'), 31.88 (t, C-14'), 29.44 (t, C-5' to C-11' and C-13'), 29.10 (t, C-12'), 25.33 (t, C-4'), 22.6 (t, C-15') and 14.03 (q, C-16'); MS : m/z 285 (M^+ - 31).

General procedure for the synthesis of epoxides, 21,22,23 and 27:

A mixture of 50% aqueous NaOH (30ml), epichlorohydrin (200 mmol) and ter.butyl ammonium hydrogen sulphate (TBAHS) (0.4 g) was vigorously stirred at 0°C for half an hour and allowed to reach room temperature. To this mixture the corresponding alcohol (50 mmol) was gradually added for 30 minutes at room temperature. The progress of the reaction was monitored by TLC. After 3h the reaction mixture was quenched with water. The aqueous phase was extracted with diethyl ether (3 x 25 ml) and the organic phase was dried over Na_2SO_4, filtered, evaporated and purified by column chromatography to provide the respective epoxides.

4-(Oxiranylmethyloxymethyl)-2,2-dimethyl-1,3-dioxalane (21).

ν_{max} (film)/cm^{-1} : 3010, 1265, 920 (CH_2-O-CH_2), 850 (terminal epoxide);

^1H NMR ($CDCl_3$, 300MHz) δ : 1.36-1.44 (4s, 12H, >C(CH_3)$_2$), 2.59-2.70(m,2H, H-9,9') , 2.81(t, 1H, J = 4.35 Hz, H-9), 2.91 (t, 1H, J = 4.35 Hz, H-9'), 3.16 (m, 1H, H-8), 3.25 (m, 1H, H-8'), 3.38-3.86 (m, 12H,H-5,6,7 &H-5',6',7'), 4.02 (m,1H,H-4), 4.29(m,1H,H-4') ;

^{13}C NMR ($CDCl_3$,75MHz) δ : 25.36(q), 26.72(q), 44.09(t), 50.76(d), 66.58(t), 72.30(t), 72.43(t), 74.71(d).

2-Propynyloxymethyloxirane (22)

ν_{max} (film)/cm^{-1} : 3300 (C≡C-H), 2100 (C≡C).1110 (CH-O-CH), 850 ;

^1H NMR ($CDCl_3$, 300MHz) δ : 2.49 (t, 1H, J = 2.38 Hz, C≡C-H), 2.64 (dd, 1H,J= 4.03,4.94 Hz , H-1), 2.81 (dd, 1H, J=4.03, 5.13Hz,H-1), 3.17(m, 1H, H-2), 3.48(m, 2H, H-3), 4.21(dd, 2H, J = 2.38, 2.30Hz, H-4)

Propyloxymethyloxirane (23)

ν_{max} (film)/cm^{-1} : 3030, 1265, 920 (CH-O-CH), 850;

^1H NMR(60 MHz,$CDCl_3$)δ:1.0(t, 3H, H-6), 1.6(q, 2H, H-5), 2.6-2.9(m, 2H, H-1) , 3-3.7(m, 5H, H-4,3,2).

3(S),7(Z)-dimethyl oct-6-enyl oxymethyloxirane (27)

ν_{max} (film)/cm^{-1} : 3010, 1380, 1370, 920 (CH-O-CH), 840 ;

^{1}H NMR(300 MHz,$CDCl_3$)δ : 0.83-2.18(m ,CH_3,CH_2,CH), 2.60(dd, 1H, J=2.75, 4.40Hz, H-1'), 2.78(dd, 1H, J=4.03, 4.95Hz, H-1''), 3.14(m,1H, H2'), 3.37(ddd, 1H, H-4'), 3.54(m,2H, H-3), 3.70(ddd, 1H, H-4''), 5.08(m, 1H, H-9).

General Procedure for coupling the epoxide with the alcohols:

Sodium hydride, 50% in petroleum wax (2.3 mmol) was washed with dry hexane under nitrogen atmosphere and to it DMSO (5 ml) was added. To the above solution, propargyl alcohol (5 mmol) in DMSO was added at 0°C for a period of half an hour under vigorous stirring and continued for 1h at room temperature. To the reaction mixture the corresponding epoxides (3 mmol) in THF (10ml) was added drop wise over a period of 30 minutes at 0-5°C. It was stirred for five more hours. The reaction was monitored by TLC, quenched with water and extracted with ether (3 x 25 ml). The ether extract was then washed with brine, dried over sodium sulphate and concentrated under *vacuo* to give the corresponding coupled products. They were purified by column chromatography with ethyl acetate and petroleum ether as eluants to furnish the pure compound.

4-[(2-hydroxy-3-propynyloxy)propyloxymethyl]-2,2-dimethyl-1,3-dioxalane (24)

ν_{max} (film)/cm^{-1} : 3450(OH), 3300(C≡C-H), 2100(C≡C), 1390 and 1380(>$C(CH_3)_2$) ;

^{1}H NMR ($CDCl_3$, 300MHz) δ : 1.36 (s, 3H, >$C(CH_3)_2$), 1.42 (s, 3H, >$C(CH_3)_2$) , 2.46 (t, 1H, J = 2.38 Hz, -C≡C-H), 3.47-4.1(m,10H,-CH and CH_2-), 4.2(d, 2H, C≡C-CH_2) ;

^{13}C NMR ($CDCl_3$,75MHz) δ: 25.09(q), 26.43(q), 58.27(t) ,66.26(t), 69.03(t), 70.76(t), 72.15(t), 72.54(t), 74.41(d), 74.62(d), 79.25(dt), 109.16(s).

4-[(2-hydroxy-3-propyloxy)propyloxymethyl]-2,2-dimethyl-1,3-dioxalane (25)

ν_{max} (film)/cm^{-1} : 3400, 1370 & 1380 ;

^{1}H NMR ($CDCl_3$, 300MHz) δ : 0.92(t,J=5.49Hz,3H, H-12), 1.36 & 1.43(2s, 6H,>$C(CH_3)_2$), 1.59(sextet,2H, H-11), 3.40-4.3(m,12H, H-4,5,6,7,8,9,10) ;

^{13}C NMR ($CDCl_3$,75MHz) δ: 10.42(q), 22.72(t), 25.32(q), 26.66(q) 66.52(t), 69.41(d), 71.59(t), 72.42(t), 72.93(t), 73.17(t), 74.67(d), 109.43(s).

4-[(2-methoxy-3-propyloxy)propyloxymethyl]-2,2-dimethyl-1,3-dioxalane (26)

ν_{max} (film)/cm^{-1} : 3000, 1370 & 1380 ;

^{1}H NMR ($CDCl_3$, 300MHz) δ : 0.92(t, J=5.47Hz, 3H, H-12), 0.93(t, J=5.49Hz, 3H, H-12'), 1.34(2s, 6H, >$C(CH_3)_2$), 1.377(2s,6H,>$C(CH_3)_2$), 1.39-1.51(m,6H, H-11 & H-11'), 3.38(s,OCH_3), 3.47(s,OCH_3), 3.34-4.25(m,24H,H-4,5,6,7,8,9,10).

2,2-dimethyl-4-[2'-hydroxy-3-(3(S),7(Z)dimthyloct-6-enyloxy)propyloxymet-hyl]-1,3-dioxalane (28)

ν_{max} (film)/cm^{-1} : 3400, 3000, 1370 & 1380 ;

^{1}H NMR ($CDCl_3$, 300MHz) δ : 1.22-1.74(m,20H), 3.40-4.18(m,2 x 12H), 5.12(bt, Vinylic H).

MS: m/z 344(M^+, 100), 329(39), 205(40), 136(86), 119(48), 101(71), 81(50).

2,2-dimethyl-4-[2'-methoxy-3-(3(S),7(Z)dimethyloct-6-enyloxy)propyloxymethyl]-1,3-dioxalane (30/32)

ν_{max} (film)/cm^{-1} : 3400, 1370 & 1380 ;

^1H NMR ($CDCl_3$, 300MHz) δ : 1.22-1.74(m,2 x 20H), 3.39(s,OCH_3), 3.42-4.29(m, 2 x 12H), 3.41(s,OCH_3), 5.09(t, J=3.68Hz, Vinylic H), 5.36(t, J= 3.69Hz, vinylic H) ;

^{13}C NMR ($CDCl_3$,75MHz) δ: 23.86-28.43(5q), 59.31(d), 60.35(d), 66.24(t), 67.6(d), 73.24(t), 75.07(t), 76.31-77.65(t), 79.52(d), 109.54(s), 110.46(s).

Hydrogenation of 24

To a solution of **24** (0.1g) in methanol Dowex 50Wx8 (0.05g) and 10% Pd/C were added and kept stirring for 24h at 3 atm pressure of hydrogen. The reaction mixture was filtered through G-4 sintered crucible using celite and the filtrate was concentrated under *vacuo* to give a yellow liquid. It was purified by column chromatography using ethyl acetate and petroleum ether as eluants to provide **18.**

3-[2-hydroxy-3-propyloxy-]propyloxy propane-1,2-diol (18)

To a solution of **17**(0.1g) in methanol (15 ml), two drops of concentrated sulphuric acid or Dowex 50wx8(0.05gm) was added. The reaction mixture was stirred for half an hour. Sodium bicarbonate was added. The solution was then filtered, dried and evaporated under *vacuo* to provide **10**.

ν_{max} (film)/cm^{-1} : 3450 (broad -OH band), 1100 (CH-O-CH-) ;

^1H NMR ($CDCl_3$, 300MHz) δ :0.98(t, 3H, H-9), 1.4(m, 2H, H-8), 2.1(-OH proton), 3.2-4.2(m, OCH_2- & OCH-); MS: m/z, 208(M^+).

3-[2-methoxy-3-propyloxy-]propyloxy propane-1,2-diol (19)

ν_{max} (film)/cm^{-1} : 3400 (broad -OH band), 3000(C-H), 1100 (CH-O-CH) ;

^1H NMR ($CDCl_3$, 300MHz) δ : 0.92(t,6H,J= 7.33Hz, H-9,9'), 1.25(s,OH), 1.58(m, 4H, H-8,8'), 3.39(s,OCH_3), 3.47(s, OCH_3), 3.35-3.99(m, OCH-).

3-[2-hydroxy-3[2(S),6(Z)-dimethylhept-5enyloxy]propyloxypropan-1,2-diol (31/33)

ν_{max} (film)/cm^{-1} : 3400 (broad -OH band), 3000(C-H) ;

^1H NMR ($CDCl_3$, 300MHz) δ : 1.25-1.73(m, 2 x 14H, >$C(CH_3)_2$ & CH_2), 3.40(s,OCH_3), 3.43(s,OCH_3), 3.40-4.3(m,2 x 12H), 5.10 & 5.39(1H, vinyl H);

MS: m/z, 344(M^+, 100), 329(39), 205(40), 136(86), 119(48), 101(71), 81(50).

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