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Reaction of Epoxides with Activated DMSO Reagent. General Method for synthesis of α-Chlorocarbonyl Compounds: Application in Asymmetric Synthesis of (3*S*)-2,3-Oxidosqualene

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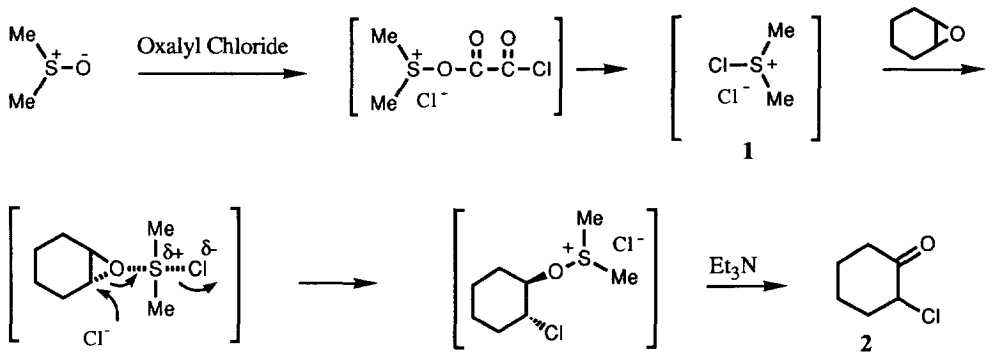
Abstract: Reaction of a variety of epoxides with DMSO-Oxalyl chloride in the presence of a catalytic amount of methanol and a base was studied. Disubstituted epoxides gave α-chloroketones in high yields. Aliphatic terminal epoxide underwent opening reaction to provide α-chloroketone as a major product. Trisubstututed epoxides provided α-chloroketones as major products through the formation of more stable carbocation. In case of a homoallylic alcohol, enedione was obtained. The efficiency of the method was shown by applying it to the enantioselective synthesis of (3*S*)-2,3-oxidosqualene.

Conversion of α-haloketones to optically active epoxides *via* enantioselective reduction[1] is an important transformation in organic synthesis. One of the most common methods in acquisition of the haloketones involves the oxidation of corresponding α-halohydrins[2] which could be prepared, either from olefins[3] or from epoxides[4,5]. Although there have been several reports for direct conversion to α-haloketones from ketones[6], olefins[7], epoxides[8], and nitroepoxides[9], there is still a need for a milder method for synthesis of α-haloketones in sensitive and complex molecules. In this paper we report a detailed account of our work for this kind of conversion through the use of DMSO and oxalyl chloride in the presence of a catalytic amount of methanol and excess of triethylamine.[10] The efficiency of the methodology has been demonstrated by synthesizing optically active 2,3-oxidosqualene which is a biosynthetic precursor for steroids and triterpenoids. We also report that the same reagent can be used to prepare enedione system from epoxy homoallylic alcohol.

Ring cleavage of epoxides to α-chlorohydrins and chloroketones using thioanisole-chlorine complex was first reported by Nakai and Kurono.[8a] They have reported that trisubstituted epoxides gave 1:1 mixture of chlorohydrins as regioisomers where secondary alcohol is oxidized to chloroketone and tertiary alcohol remains intact. Terminal epoxides, under the same conditions, gave 3:1 ratio of chloroketone and chloroaldehyde. These results show that the reaction is not regioselective. Later on, Olah and co-workers[8b] reported similar ring opening of few disubstituted epoxides with dimethylsulfide-chlorine or bromine complex. As a part of our programme in asymmetric synthesis area[1,11], we thought that a mild and versatile method for the conversion of racemic-epoxides to α-chloroketones would be useful in the preparation of chiral epoxides.

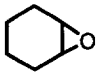
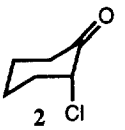
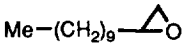
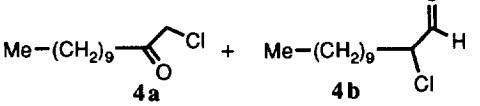
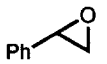
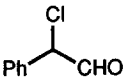
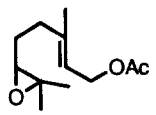
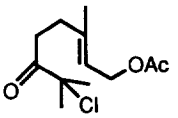
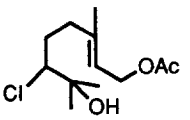
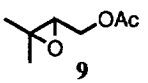
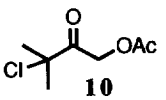
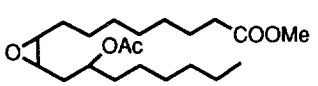
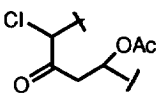
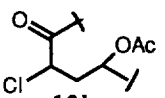
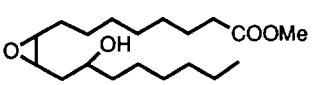
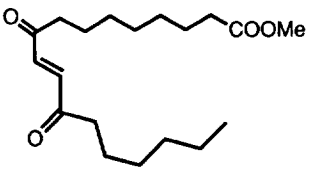
With this aim, we turned our attention towards activated DMSO reagents. During Swern oxidation[12] of an alcohol to ketone, activation of DMSO is usually done with an electrophilic reagent, *e.g.* oxalyl chloride. The DMSO reacts with oxalyl chloride in exothermic manner and produces chlorodimethylsulfonium salt **1**. The reaction of this salt with an alcohol gives rise to alkoxysulfonium salt which reacts with base to provide carbonyl compound and dimethyl sulfide. We envisaged that if an epoxide is treated with the sulfonium salt **1**, their co-ordination will facilitate the nucleophilic attack of chloride ion on epoxide carbon to provide α-chloroalkoxysulfonium salt , which, on reaction with base, would provide α-chloroketone. It was indeed the case. When cyclohexene oxide was treated with DMSO and oxalyl chloride complex at -60° C followed by triethylamine, 2-chloro cyclohexanone **2** was obtained in 93% yield (Scheme I).



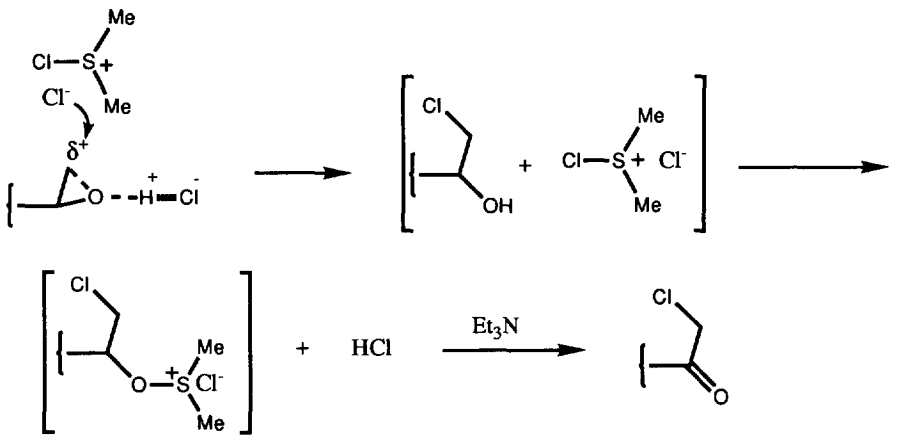
Scheme I

Surprisingly, some acyclic epoxides failed to react under the conditions described in scheme I. However, we observed that upon addition of 10-20 mole % of methanol along with the substrate, those epoxides were also cleaved satisfactorily. In order to have uniformity, a catalytic amount of MeOH was used for all the epoxides and the results are shown in table 1. Methanol presumably reacts with the chlorosulfonium salt **1** to give alkoxysulfonium salt and HCl. The liberated HCl catalyzes the ring opening reaction. If the HCl is fully responsible for opening of the epoxides, one expects formation of secondary carbocation over primary one in monosubstituted terminal epoxides. However, the product obtained is otherwise. The terminal epoxide **3** gave chloro ketone **4a** as the major product along with 6% of chloro aldehyde **4b**. The co-ordination of HCl with the epoxide facilitates the nucleophilic attack of chloride ion from the least hindered side. It is assumed that complete formation of carbonium ion does not take place, and the reaction proceeds *via* S_N2 mechanism (Scheme II).

Table 1: Reaction of Epoxides with DMSO-ClCOCOCl-MeOH-Et_3N in CH_2Cl_2 at -60° C.[a]

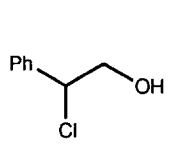
Epoxides	Products	Isolated Yield (%)
	 **2**	93[b]
 **3**	 **4a** : **4b** 94 : 6	88[c]
 **5**	 **6a**	80[d]
 **7**	 **8a**  **8b** 54% Yield 20% Yield	74
 **9**	 **10**	90[e]
 **11**	 **12a**  **12b**	74[c]
 **13**	 **14**	40

[a] Usually, 20 mol% of MeOH was used in all the examples. [b]MeOH addition is obligatory. [c]Yield for inseparable mixture. [d]The chloroaldehyde could not be obtained in very pure form due to its decomposition. [e] Chloroketone is the only product formed in this reaction and other isomeric product is not seen at all.

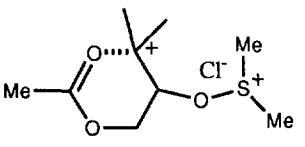


Scheme II

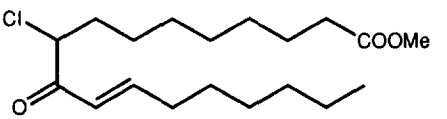
The ring opening in case of styrene oxide gave chloroaldehyde **6a** as the only product. Although we were unable to purify this compound because of its instability[8a], its identity was confirmed by crude ^{1}H-NMR and by intercepting the reaction to the corresponding chlorohydrin **6b** stage. The structure of chlorohydrin was confirmed by synthesizing authentic sample from styrene oxide and $FeCl_3$ in ether.[4a] The Swern oxidation of the chlorohydrin **6b** showed the similar decomposition pattern. The ring opening of trisubstituted epoxides proceeded only when catalytic amount of methanol is added. Epoxy geranylacetate **7** gave a mixture of chloroketone **8a** and chlorohydrin **8b** in the ratio of 3:1. In this case, formation of **8a** is prevalent because the greater stability of tertiary carbocation governs the mode of opening. This is clearly shown in case of the epoxide **9** where chloroketone **10** is the sole product. Here, the carbocation formed after the co-ordination with HCl is stabilized by the acetoxy group *via* a 6-membered ring, as depicted in assembly **10a** .



6b



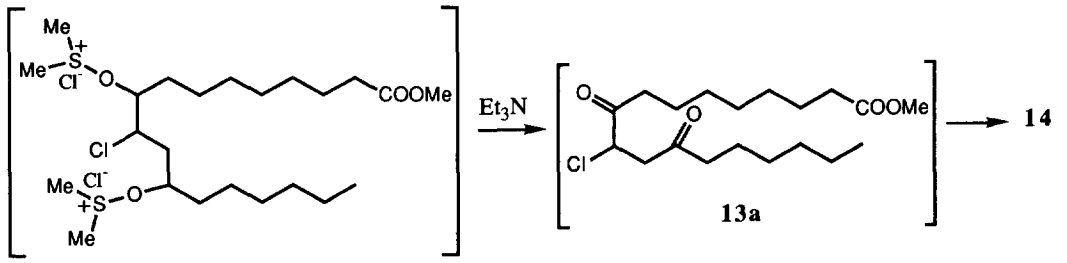
10a



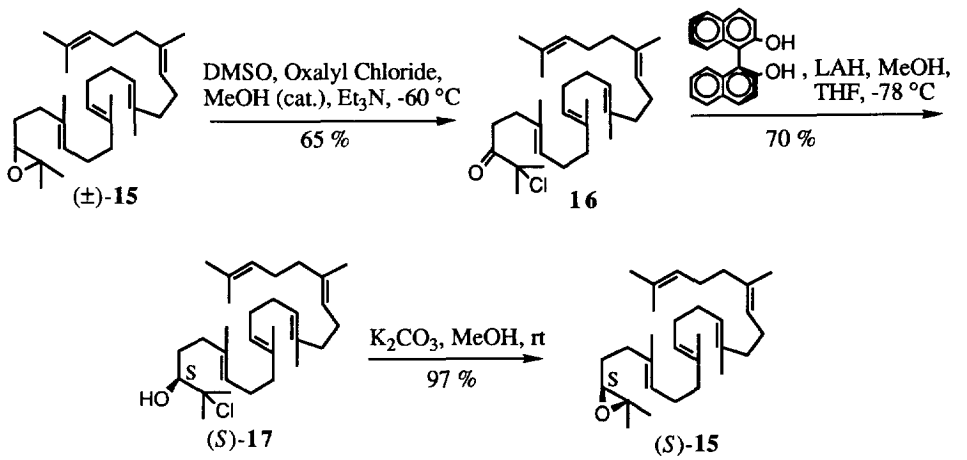
12c

In the case of homoallylic epoxyacetate **11**, we obtained 1:1 a mixture of α-chloroketones **12a** & **12b** in 74% yield and enone **12c** in 11% yield. Most probably the **12c** is formed from **12a** *via* base induced dehydroacetoxylation reaction. When the hydroxyl group was unprotected as in **13**, the major isolated product was enedione **14**, which might be forming *via* base catalyzed dehydrohalogenation of the initially formed

chlorodiketone **13a**. However, despite our all efforts, we could not isolate and characterize other minor products. Since the substrate already had a hydroxyl group, methanol addition was not required. The geometry of the double bond in **14** was assumed to be *E* due to its greater stability.[13] In view of the absence of coupling of the olefinic protons in ^{1}H-NMR spectrum, it is assumed that the environment around the enedione unit of the molecule is symmetrical.

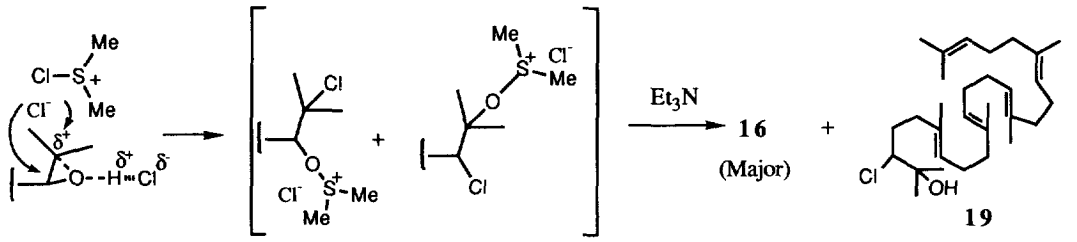


The efficiency of this methodology for conversion of epoxides to α-chloroketones is shown by synthesizing (3*S*)-2,3-oxidosqualene (Scheme III) which is a very important and versatile biosynthetic precursor of steroids and polycyclic triterpenoids.



Scheme III: Enantioselective Synthesis of (3*S*)-2,3-Oxidosqualene

Treatment of racemic-2,3-oxidosqualene (±)-**15** with DMSO-oxalyl chloride in the presence of 20 mol% methanol followed by Et_3N gave α-chloroketone **16** in 65% yield. During the reaction, chlorohydrin **19** was also formed in ~10% yield.[14] Formation of these products is explained in scheme IV. Ketone **16** was treated with (*S*)-BINAL-H[15,16] (-78 °C, THF, 7h) and the alcohol (*S*)-**17** was obtained in 65-70% yield. ^1H NMR analysis of Mosher ester[17] of the the alcohol (*S*)-**17** showed that it was contaminated with 15.5% of the (*R*)-**17** isomer. Although the enantioselectivity was moderate, the BINAL-H reduction of chloroketone of this type, to the best of our knowledge, has not been looked at as yet. Ring closure of (*S*)-**17** with base (K_2CO_3, MeOH) provided (3*S*)-2,3-oxidosqualene **15**[18] (Scheme III). The absolute stereochemical course in the reduction of **16** with BINAL-H, predicted from the mechanistic model[15], was confirmed by optical rotation of the epoxide (*S*)-**15**.



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Scheme IV: Mechanism for the Formation of α-Chloroketone

In summary, we have shown here that epoxides can directly be converted to α-chlorocarbonyl compounds in high yields. We have also shown that enedione type system can be synthesized directly from homoallylic epoxyalcohol. We have applied the methodology in an enantioselective synthesis of (3*S*)-2,3-oxidosqualene, an important biosynthetic precursor.

Experimental Section

^1H NMR spectra were recorded on Jeol and Brucker, as mentioned in the experimentals, using TMS as internal standard. Chemical shifts are reported in ppm, and coupling constants are reported in Hz. IR spectra were recorded on Perkin-Elmer 580 and 1320 spectrometers. Optical rotations were taken on a Jasco DIP-370. Routine monitoring of reactions was performed using silica gel-G obtained from Acme. All the chromatographic separations were done by using silica gel (Acme's, 60-120 mesh). All the reactions were run under an atmosphere of dry nitrogen or argon using flame-dried glassware and freshly distilled and dry solvents from solvent stills. The organic extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*.

General Procedure for Epoxide opening Reaction: Oxalyl chloride (3 - 4 mmol) was added to a solution of DMSO (3 - 4 mmol) in CH_2Cl_2 (10 ml) at -60°. The reaction mixture was stirred for 5 min and then epoxide (1 mmol) and methanol (0.20 mmol) in 2 ml CH_2Cl_2 were added. After stirring for 30 min at the same temperature, triethylamine (7 - 8 mmol) was added and the mixture was stirred for 30 min and then allowed to warm to room temperature (45 min). Water (20 ml) was added, and the mixture was extracted with CH_2Cl_2 (20 ml X 2). The organic layers were combined and washed with water, brine, and dried. The solvent was removed on rotavap and the crude product was chromatographed on silica gel with EtOAc in pet-ether to give pure α-chlorocarbonyl compound or product derived from that.

2-Chlorocyclohexan-1-one 2: 490 mg (5.0 mmol) of cyclohexene oxide provided 620 mg (93% yield) of α- chloro ketone **2**[9] as a colourless liquid after purification by column chromatography; R_f 0.49 (10% EtOAc in Pet.-ether); FTIR (film) 1726 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ1.55 - 2.20 (m, 5H), 2.21 - 2.55 (m, 2H), 2.60 - 2.95 (m, 1H), 4.39 (ddd, J = 8.6, 5.0, 1.4 Hz).

1-Chlorododecan-2-one 4a: 184 mg (1.0 mmol) of 1,2-epoxydodecane **3** gave 193 mg (88 % yield) of **4a** and **4b** in the ratio of 94 : 6 as an inseparable liquid. The compound **4a** could be obtained in pure form by careful column chromatography; FTIR (film) 1722.6 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ0.88 (t, J = 7.0 Hz, 3H), 1.25 (bs, 14 H), 1.62 (m, 2H), 2.58 (t, J = 7.3 Hz, 2H), 4.05 (s, 2H). Anal. Calcd for $C_{12}H_{23}OCl$: C, 65.90; H, 10.53; Cl, 16.25. Found: C, 65.68; H, 10.64; Cl, 16.32.

The minor compound **4b** could not be purified but its presence was noticed based on the presence of two sets of peaks in ^1H NMR spectrum; δ4.12 (ddd, J = 8.2, 5.6, 2.5 Hz), 9.48 (d, J = 2.4 Hz).

Ring Opening of Styrene Oxide: Styrene oxide (240 mg 2.0 mmol) was treated with activated DMSO reagent as described in the general procedure. After work-up, the crude material was filtered over a small plug of silica gel and 224 mg of chloroaldehyde was obtained as an oil. Tlc of the material showed decomposition so pure material could not be obtained but a doublet at δ9.76 alongwith aromatic protons in ^1H NMR spectrum indicated the presence of chloroaldehyde. When the reaction was intercepted by adding water, instead of Et_3N, at -60 °C, corresponding chlorohydrin **6b**[4a] was obtained as an oil; ^1H NMR (CCl_4, 60 MHz) δ2.68 (bs, 1H, -OH), 3.77 (d, J = 7 Hz, 2H), 4.87 (t, J = 6.5 Hz, 1H), 7.35 (aromatic, 5H).

[E]-8-Acetoxy-2-Chloro-2,6-dimethyl-oct-6-en-3-one 8a: 200 mg of the epoxy geranylacetate gave 125 mg (54% yield) of the product alongwith 50 mg (20% yield) of chlorohydrin **8b**. Compound **8a** was characterized as colourless liquid; R_f 0.51 (15 % EtOAc in pet.-ether); I.R. (film) 1720 cm^{-1} (broad peak); ^1H NMR (CCl_4, 60 MHz) δ1.57 (s, 6H), 1.71 (s, 3H), 1.94 (s, 3H), 2.31 (m, 2H), 2.77 (m, 2H), 4.43 (d, J = 7.0 Hz, 2H), 5.27 (m, 1H). Anal. Calcd for $C_{12}H_{19}O_3Cl$: C, 58.42; H, 7.71; Cl, 14.40. Found: C, 58.28; H, 7.84; Cl, 14.48.

Compound **8b** was characterized as; R_f 0.22 (15 % EtOAc in pet-ether); IR (film) 3450, 1722 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ1.22 (s, 6H), 1.67 (s, 3H), 1.95 (s, 3H), 2.20 (t, J = 5.5 Hz, 2H), 3.57 (dd, J = 10, 2.2 Hz, 1H), 4.42 (d, J = 7Hz, 2H), 5.25 (t, J = 6.5 Hz, 1H).

4-Acetoxy-2-chloro-2-methylbutan-2-one 10: 144 mg (1.0 mmol) of the epoxide **9** was subjected to DMSO-ClCOCOCl-MeOH-Et_3N, as mentioned in the general procedure, to afford 160 mg (90 % yield) of the product **10**; FTIR (film) 1736, 1755 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ1.74 (s, 6H), 2.18 (s, 3H), 5.14 (s, 2H). Anal. Calcd for $C_7H_{11}O_3Cl$: C, 47.06; H, 6.16; Cl, 19.89. Found: C, 47.22; H, 6.44; Cl, 19.94.

Ring Opening of homoallylic epoxyacetate 11: 300 mg (0.81 mmol) of the epoxyacetate **11** was

opened-up, as described, in the general procedure. The major product (244 mg, 74% yield) was obtained as a 1:1 mixture of chloroketones **12a** & **12b**; R_f 0.5 (10 % EtOAc in pet-ether); IR (film) 1725 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ0.91 (t, J = 6.0 Hz, 3H), 1.4 (bm, 20H), 2.0 (s, 3H), 2.2 (m, -C$\underline{H_2}$-COOMe; -C$\underline{H_2}$-CO- of **12b**), 2.62 (m, -CO-HCCl-C$\underline{H_2}$-CHOAc-), 2.87 (d, J = 6 Hz, -ClCH-CO-C$\underline{H_2}$-CHOAc-), 3.65 (s, 3H), 4.2 (m, 1H), 5.05 (m, 1H). The minor compound **12c** (10% yield) was characterized as; IR (film) 1728, 1687 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ0.91 (t, J = 6.0 Hz, 3H), 1.4 (bm, 20H), 2.2 (m, 4H), 3.65 (s, 3H), 4.2 (t, J = 7 Hz, 1H), 6.45 (d, J = 16 Hz, 1H), 7.0 (dt, J = 16, 6.5 Hz, 1H).

Reaction of methyl ricinoleate epoxide with DMSO-ClCOCOCl-Et$_3$N: The epoxide **13** (500 mg, 1.5 mmol) was treated with DMSO-ClCOCOCl reagent in the same way as described in the general procedure except that MeOH was not used in this case. After purification, 200 mg (40% yield) enedione **14** was obtained as an oil; R_f 0.42 (10 % EtOAc in pet.-ether); FTIR (film) 1678, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ0.89 (t, J = 6.9 Hz), 1.30 (m, 12H), 1.62 (m, 6H), 2.29 (t, J = 7.5 Hz, 2H), 2.62 (dt, J = 7.4, 1.5 Hz, 4H), 3.66 (s, 3H), 6.86 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ13.9, 22.4, 23.6, 23.7, 24.8, 28.8, 28.9, 31.5, 34.0, 40.2, 41.5, 41.6, 45.6, 51.4, 136.17, 136.25, 174.1, 200.61, 200.7; MS (CI): 325 (M^++1, 52 %), 307 (16%), 293 (100 %); HRMS calcd for $C_{19}H_{32}O_4$, 324.2301, found 324.2294.

[All E]-2-Chloro-2,6,10,15,19,23-hexamethyl-6,10,14,18,22-tetracosapentaene-3-one 16: Typically, the squalene oxide (±)-**15** (300 mg, 0.7 mmol) was treated with DMSO - oxalyl chloride-MeOH reagent as described above. 210 mg (65 % yield)) of the required product **16** as a colorless oil; R_f 0.55 (97:3 Pet.-ether : EtOAc); FTIR (film) 1718 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ1.60 (s, 12H), 1.62 (s, 3H), 1.67 (s, 9H), 1.91-2.19 (m, 16H), 2.27 (t, J = 7.7 Hz, 2H), 2.85 (t, J = 7.5 Hz, 2H), 5.14 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ15.94, 17.58, 25.60, 26.59, 26.72, 28.21, 28.67, 33.91, 35.02, 39.52, 39.68, 70.55, 124.22, 124.38, 124.41, 125.05, 131.00, 133.34, 134.72, 134.95, 204.5; MS (CI): 463 (M^++3, 16 %), 461 (M^++1, 69 %), 425 (24 %), 187 (100 %), 161 (81 %), 137 (61 %); Anal. Calcd for $C_{30}H_{49}OCl$: C, 78.18; H, 10.64; Cl, 7.71. Found: C, 78.10; H, 10.68; Cl, 7.80.

[S-(All-E)]-2-Chloro-3-hydroxy-2,6,10,15,19,23-hexamethyl-6,10,14,18,22-tetracosapentaene 17: In a small flame dried (under argon) round-bottomed flask, LAH (37 mg, 0.97 mmol) was weighed and THF (2 ml) was added. EtOH (40 mg, 0.87 mmol) solution in THF (0.5 ml) was added drop by drop at rt and stirred for 10 min. (*S*)-binaphthol (232 mg, 0.81 mmol) solution in THF (1 ml) was added slowly and further stirred for 30 min. The flask was then cooled to -78 °C and α-chloroketone **16** (100 mg, 0.22 mmol) solution in 0.5 ml THF was added and stirring was continued for 7 h at the same temperature. The reaction mixture was quenched with 100 µl MeOH and the cooling bath was removed and the flask was allowed to warm to room temperature. The reaction mixture was diluted with ether and washed with sat. aq NH_4Cl solution, water, and brine. The organic layer, after drying, was concentrated to give crude material which was chromatographed over silica gel column to give 55 mg (55% yield) of (*S*)-chlorohydrin **17** as a colourless oil; R_f 0.3 (97:3 Pet.-ether : EtOAc); $[\alpha]^{25}_D$ +10.7° (*c* 1.1, MeOH); IR (film) 3440 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ1.45 (m, 1H), 1.55 (s, 3H), 1.59 (s, 3H), 1.60 (s, 12H), 1.62 (s, 3H), 1.68 (s, 3H), 1.72 (m, 1H), 1.95-2.12 (m, 18H), 2.27 (m, 1H), 3.49 (ddd, J = 10.3, 5.4, 1.5 Hz, 1H), 5.12 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ16.01, 17.64, 25.67, 26.62, 26.65, 26.76, 27.18, 28.26, 29.15, 29.75, 36.48, 39.67, 39.72, 76.09, 78.50, 124.25, 124.42, 125.14, 131.19, 134.37, 134.87, 134.93, 135.1; HRMS calcd for $C_{30}H_{51}OCl$ 462.3629, found 462.3628. Anal. Calcd for $C_{30}H_{51}OCl$: C, 77.84; H, 11.03; Cl, 7.68. Found: C, 77.68; H,

11.16; Cl, 7.74.

Mosher ester[17] analysis of (*S*)-**17** on 400 MHz ^{1}H NMR (ratio of -OCH_3 peaks) shows its enantiomeric excess to be 69% [(*SR*)-diastereomer (δ3.53) and (*RR*)-diastereomer (δ3.49)].

[S-(All-E)]-2,2-dimethyl-3-(3,7,12,16,20-pentamethyl-3,7,11,15,19-heneicosapentaenyl)-oxirane (*S*)-15: A solution of (3*S*)-α-chlorohydrin **17** (50 mg, 0.12 mmol) in dry MeOH (2 ml) was treated with anhydrous K_2CO_3 (80 mg, 0.58 mmol) at rt for 5 h. The reaction mixture was taken into ether and washed with water, brine, and dried. Concentration under reduced pressure and purification by silica gel chromatography afforded 45 mg of (3*S*)-2,3-oxidosqualene in 97% yield as a colorless oil; R_f 0.5 (97:3 Pet.-ether : EtOAc); $[\alpha]^{25}_D$ -1.4° (*c* 2, MeOH) [lit[18c] $[\alpha]^{25}_D$ -2.0° (*c* 2, MeOH)] which corresponds to 70% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ1.26 (s, 3H), 1.30 (s, 3H), 1.60 (s, 12H), 1.62 (s, 3H), 1.68 (s, 3H), 1.95-2.2 (m, 20H), 2.70 (t, J = 6.2 Hz, 1H), 5.15 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ16.02, 17.70, 18.73, 24.88, 25.65, 26.68, 26.79, 27.50, 28.27, 36.32, 39.67, 39.73, 58.23, 64.17, 124.28, 124.42, 124.95, 131.18, 133.97, 134.88, 134.93, 135.11.

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