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N. B. Malkar [a] & V. G. Kumar [a]
[a] Hindustan Lever Research Center , Andheri-(E), Mumbai, 400099, INDIA
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ENANTIOSELECTIVE REDUCTION OF PROCHIRAL KETONES USING A REAGENT PREPARED FROM LITHIUM ALUMINIUM HYDRIDE, (+)*THREO*-1,16-DIBENZYLOXY, 7(R),8(R)-DIHYDROXY HEXADECANE AND ALCOHOL

N.B.Malkar and V.G.Kumar*
Hindustan Lever Research Center, Andheri-(E), Mumbai- 400 099, INDIA

Abstract : Asymmetric reduction of prochiral ketones to optically active chiral secondary alcohols was achieved using a reagent prepared by modifying lithium aluminium hydride with a chiral auxiliary, (+)*threo*-1,16-dibenzyloxy,7,8-dihydroxy hexadecane and various additive alcohols. (+)*threo*-1,16-dibenzyloxy,7(R),8(R)-dihydroxy hexadecane was prepared from (+)*threo*-9(R),10(R),16-trihydroxy hexadecanoic acid. Alcohols such as $CH_3(CH_2)_n$-OH of different chain length (n = 0-11) and (R)-hydnocarpic alcohol were used. Complex prepared from (+)*threo*-1,16-dibenzyloxy,7(R),8(R)-dihydroxy hexadecane, LAH and (R)-hydnocarpic alcohol reduced acetophenone in moderate enantioselectivity (maximum of 70% ee). Various arylalkylketones were reduced with the same complex.

Introduction :

The metal hydride reagents have achieved importance as the reagents of choice for performing enantioselective reduction of prochiral ketones[1]. The modification of aluminum or boron hydrides with chiral protic substances, such as chiral alcohol or amine, generates useful reagents for the reduction of prochiral ketones leading to chiral alcohols. The first attempt in enantioselective reduction of prochiral ketones was made by Bothner-By in 1951 by a complex prepared from lithium aluminum hydride (LAH)

* To whom correspondence should be addressed

and (+)camphor[2]. Successively number of reagents have been prepared by modification of LAH with alkoxides[3], sugars[4], amino alcohols[5] and other derivatives readily available from naturally occurring substances[6]. The first virtually complete enantiofacial recognition of prochiral carbonyl compounds was achieved in 1979 by Noyori where LAH is modified with optically pure 2,2'-dihydroxy-1,1'-binaphthyl (BINAL-H) and an alcohol[7,8].

As shown by Noyori, difficulty in obtaining high enantioselectivity with modified LAH reagents was because of the number of reactive species present in the different chemical and chiral environment. Thus an average selectivity depending upon the concentration, reactivity, and chiral recognition ability of each species was achieved. In order to minimize the number of reactive species (or if possible provide a single, highly selective hydride species which has complete chiral recognition ability) for obtaining high degree of enantioselectivity is a crucial step.

A rigid conformation to the reagent can be provided by mainly diols, diamino alcohols and diamines. There are many naturally occurring polyhydroxy fatty acids. (±)*threo*-9(R/S),10(R/S),16-trihydroxy hexadecanoic acid (aleuritic acid) present in the lac resin[9,10] secreted by the insect *Laccifer lacca kerr*, is probably the most abundant.

Here we report the use of (+)*threo*-1,16-dibenzyloxy,7(R),8(R)-dihydroxy hexadecane as a chiral auxiliary prepared from (+)*threo*-aleuritic acid in enantioselective reduction of prochiral ketones using LAH. The long alkyl substituents around the vicinal hydroxyl

groups was hypothesized to provide steric hindrance and thereby contributing to increased selectivity. This molecule in addition have two chiral centers and therefore was expected to give chiral recognition. Use of an alcohol added as an additive to the complex of LAH and (+)*threo*-1,16-dibenzyloxy,7(R),8(R)-dihydroxy hexadecane for improved selectivity was also demonstrated.

Results And Discussion :

We endeavored to explore utilization of a suitably end-group modified optically active variety of *threo*-aleuritic acid in enantioselective reduction by using it as a chiral auxiliary to modify LAH. In order to prepare such reagent, our efforts were to resolve the (±)*threo*-aleuritic acid to (+)*threo*-aleuritic acid (I)[11]. The (+)*threo*-aleuritic acid has functional groups other than vicinal hydroxyl, such as terminal hydroxyl and carboxyl. These groups can interfere in LAH complexation. In order to prevent this, (+)*threo*-aleuritic acid was derivatised to (+)*threo*-1,16-dibenzyloxy,7(R),8(R)-dihydroxy hexadecane ([α]=+26.3^0, concentration:0.5%, solvent:methanol) as shown in fig.1.

(+)*Threo*-1,16-dibenzyloxy,7(R),8(R)-dihydroxy hexadecane prepared was reacted with 1 equivalent of LAH to give Complex-I (fig.2). Use of this complex-I for reduction of acetophenone gave only 13% enantiomeric excess (%ee) with predominant formation of R-isomer. In order to increase the selectivity, one of the hydride atom viz. Ha or Hb, was blocked[12] by addition of an alcohol to give complex-II (fig.3).

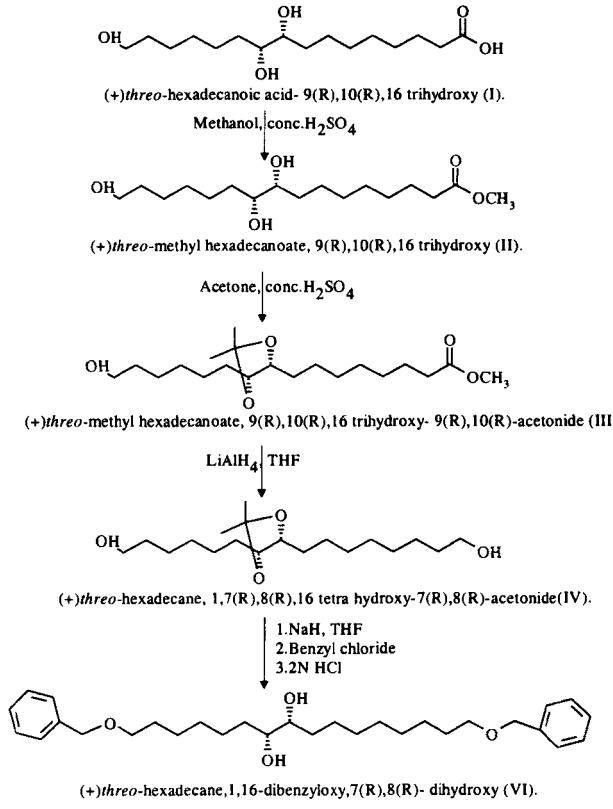


Fig.1

Synthesis of (+)*threo*-1,16-dibenzyloxy,7(R),8(R)-dihydroxy hexadecane.

Methanol was added to the complex-I in 1:1molar ratio and acetophenone was reduced with it. The 23%ee with R-isomer was achieved, an increase of only 10%ee as compared to BINAL-H where an addition of alcohol (ethanol) increased the %ee from 2 to 98. Methanol when added as an additive restricted the rotation of hydride to some extent which in turn was responsible for increase in the %ee. In an attempt to introduce increased steric hindrance in Complex-II, we tried variety of alcohols starting from

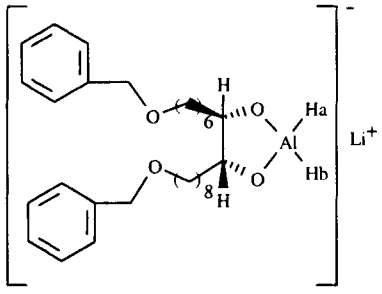


Fig.2

Complex of (+)-*threo*-1,16-dibenzyloxy,7(R),8(R)-dihydroxy hexadecane +LAH (1:1), Complex-I.

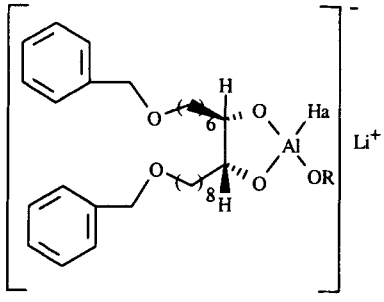


Fig.3

Structure of (+)*threo*-1,16-dibenzyloxy,7(R),8(R)-dihydroxy hexadecane + LAH + Alcohol (1:1:1), Complex-II.

ethanol (C2 alcohol) to lauryl alcohol (C12 alcohol) to (R)-hydnocarpic alcohol (C16 alcohol with cyclopentene ring). The results obtained are given in Table.1.

In all the cases studied above, R-isomer was predominantly formed. A steady increase in %ee was observed from butanol (C4 alcohol, 30%ee) to lauryl alcohol (C12 alcohol,

Table 1
Prochiral Reductions Of Acetophenone Using[a] Complex-I And Different Additives.

Additive[b,c]	configuration of alcohol, % of R	%ee[d]
--	R, 57%	13
CH_3OH	R, 61%	23
CH_3CH_2OH	R, 63%	26
$CH_3(CH_2)_2OH$	R, 65%	30
$CH_3(CH_2)_3OH$	R, 66%	31
$(CH_3)_2CH(OH)$	R, 67%	34
$CH_3(CH_2)_5OH$	R,70%	40
$CH_3(CH_2)_7OH$	R, 74%	48
$CH_3(CH_2)_{11}OH$	R, 83%	66
3-Hexanol	R, 73%	46
(R)-Hydnocarpic alcohol[e]	R, 85%	70

a:reductions were carried out using 1:4 equivalents of reagent at -78^{0}C for 7-9hrs. b:1equivalent of additive alcohol added to 1 equivalent of complex-I, purity of additive alcohols>99% by GLC, c:conversion >45% based on GLC (column: 5%DEGS 9ft/DB-FFAP 30m), d:based on chiral HPLC column, KROMASIL-100-5CHI-1,e: prepared as per procedure[13].

66%ee). A maximum of 70%ee was obtained when (R)-hydnocarpic alcohol (C16 alcohol) was used. This trend is exemplified in the plot of %ee vs number of carbon atom in the alcohol (fig.4). Thus the carbon length of an alcohol is found to be influencing the steric factor which restricts the free rotation of hydride species and reduce the number of hydride species leading to formation of one isomer predominantly. A further increase in the length of additive alcohol did not increases %ee.

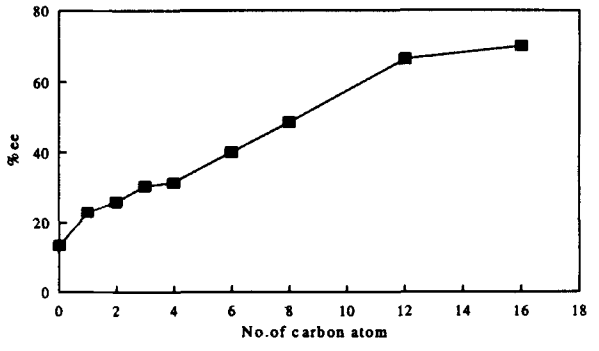


Fig.4.

Effect of number of carbon atoms on %enantiomeric excess.

When reduction of acetophenone was carried out at different temperatures using complex-II (where (R)-hydnocarpic alcohol was used as an additive alcohol), it was observed (as expected) that %ee was decreasing as the temperature was raised from -78 to 30^{0}C. A plot of observed selectivity, ln(R/S) vs 1/T(in ^{0}K) was non linear as shown in fig.5. Maximum optical yield (70%) was obtained when the temperature was at -78^{0}C.

A series of arylalkylketones were reduced to arylalkylcarbinols using the same complex. All reaction were carried out under similar conditions. The complex-II was prepared by addition of (+)*threo*-1,16-dibenzyloxy,7(R),8(R)-dihydroxy hexadecane, followed by (R)-hydnocarpic alcohol to LAH solution at 0^{0}C, and refluxing it for 90 minutes in dry THF under inert atmosphere. Thus prepared complex-II was then cooled to -78^{0}C and

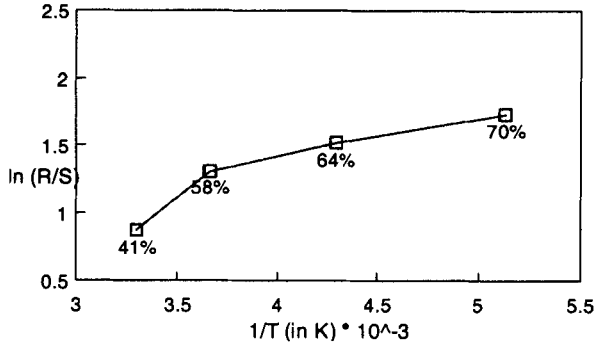


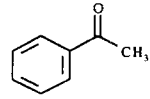
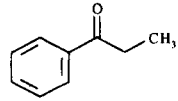
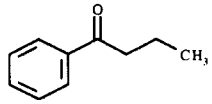
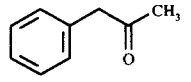
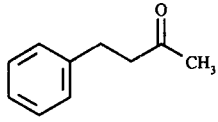
Fig.5.

Effect of temperature on %ee.

different prochiral ketones were reduced for 7-9 hrs. The chiral auxiliary was recoverd by crystalisation from hexane in 94% yield. The results obtained were given in Table.2.

These results show that, in the case of ketones where phenyl group is directly attached to carbonyl group more or less the same (68-70)%ee was observed, but in the case of ketones, where one or more than one methylene group is present separating the phenyl group and the carbonyl group, low (21-32) %ee was observed. In all these cases the R-isomer was predominantly formed. The predominant formation of R-isomer could be explained[15] via. a six membered transition state model. In the transition state model (fig. 6) (formed by reaction of acetophenone with complex-II (where R' = hydnocarpic alcohol)) oxygen of the R'O group, due to it's highest basicity among the three oxygens attached to Al, acts as the bridging atom. In chair conformation, methyl group takes up axial position while phenyl group takes up equatorial position and thereby favor formation of R-isomer.

Table 2
Enantioselective reduction of arylalkylketones[a].

Arylalkylketone	Arylalkylcarbinols[b]		
	$[\alpha]_{obs.}$[c] (solvent,concentration)	Configuration[d]	%ee[e]
	+29.8 (ethanol,5)	R	70
	+31.5 (acetone,6.9)	R	68
	+30.1 (benzene,2.98)	R	69
	-10.8 (chloroform,4.0)	R	32
	-4.1 (benzene,4.7)	R	21

a.reactions were carried out using 1:4 equivalents of reagent (Complex-I: (R)-hydnocarpic alcohol (1:1), at -78^{0}C for 7-9hrs), b:conversion >80% based on GLC(column: 5%DEGS 9ft/ DB-FFAP 30m), c:measured using JASCO-Polarimeter. d:ref.[14] e:based on chiral HPLC column, KROMASIL-100-5CHI-1.

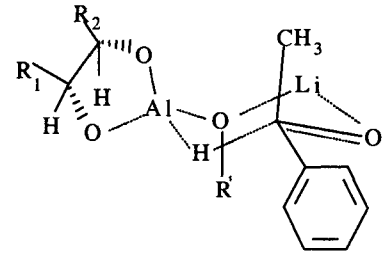


Fig.6

Transition state model for hydride transfer mechanism.

Experimental:

All m.p.s are uncorrected. Optical rotations were measured on the Jasco DIP-20 polarimeter (Glass cell, length:100mm). I.R. spectra were recorded using BOMEM Infrared Spectrophotometer in potassium bromide. ^{1}H and ^{13}C NMR NMR spectra were recorded on 200.13 MHz Bruker spectrometer. CD_3OD and $CDCl_3$ were used as solvents & tetramethylsilane as an internal standard, chemical shifts are expressed in δ-units. HPLC was carried out using Shimadzu SCL instrument: Column: Phenomenex, BONDCLONE-C18, stainless steel 25cm×0.46cm, 10m; Mobile phase: methanol; Flow rate: 0.5mL/min.; Detector: R.I. (Perkin Elmer LC-30). Chiral HPLC analysis was carried out on KROMASIL-100-5CHI-1 column (eluent: 2-propanol / n-hexane = 10/90). GLC analysis was carried out on columns: 5%DEGS 9ft / DB-FFAP 30 mts. THF was dried by distilling over Na metal using benzophenone as an indicator. Freshly distilled THF was used for all the reactions. All glass apparatus was oven dried at 110^0C for 2-4hrs and then flushed with dry nitrogen. 1M LAH solution in THF was supplied by Aldrich Co. and was kept under dry nitrogen and was standardized[16] prior to use. (±)*threo*-Aleuritic acid supplied by Pond's (INDIA) limited, Madras was crystallized twice with 50% aqueous ethanol to give (±)*threo*-aleuritic acid of required purity (99%). The (±)*threo*-aleuritic acid was resolved by (-)brucine to get (+)*threo*-aleuritic acid [α]=+27.2^0(concentration:0.5% in methanol), M.P.=101-103^{0}C. Enantiomeric purity of (+)*threo*-aleuritic acid was determined using Europium tris[3-(trifluoromethyl-hydroxymethylene)(+)camphorate] shift reagent[17].

(+)*threo*-methyl 9(R),10(R),16 trihydroxy-hexadecanoate(II): In a three neck

round bottomed flask fitted with stirrer and reflux condenser (+)*threo*-9(R),10(R),16-trihydroxy hexadecanoic acid, I (10 g, 0.032 M) was taken. To this methanol(100 mL) was added and then solution was acidified using conc. sulphuric acid (0.5 g). Reaction mixture was refluxed for 9 hours, and during which reaction was monitored using TLC(Solvent system:-Chloroform: Methanol::9:1). It was then cooled to room temperature and potassium carbonate (5%) solution was added to make pH neutral. Methanol was distilled off, water (100 mL) was added to the residue under stirring and then reaction mixture temperature was maintained between 0 and 5^0C for 5hours. The solid obtained was filtered and washed with water and dried under vacuum to give II [9.3 g, yield=88.91%, $[\alpha]=+24.6^0$ (c=0.5, methanol), M.P.:71-72^0C].

IR(KBr)υ_{cm-1}:1740.17cm^{-1}(-COOCH$_3$).,

^{1}HNMR: 3.66ppm (s,3H,-COOCH$_3$), 3.64ppm (t,J=5.24,2H,-CH$_2$-OH), 3.39ppm (bs,2H,-CH(OH)-CH(OH)-), 2.30ppm (t,J=7.44,2H,-CH$_2$-COOCH$_3$), 1.61ppm,1.31ppm (s,22H,-CH$_2$-).

(+)*threo*-methyl 9(R),10(R),16 trihydroxyhexadecanoate - 9(R),10(R)-acetonide (III): In three necked flask fitted with stirrer, reflux condenser and calcium chloride guard tube, (+)*threo*-methyl 9(R),10(R),16 trihydroxy-hexadecanoate, II (9 g, 0.028 M) was taken in dry acetone (90 mL). Then solution was acidified with conc. sulphuric acid (0.5 g) and the reaction was monitored using TLC (solvent-system, Chloroform +Methanol : 9+1). After 4 hours, the reaction mixture was neutralized by K_2CO_3 solution (5%). Two layers were observed and without separation of layers acetone was stripped off. To this water (100 mL) was added and extracted thrice with solvent ether

(3 × 100 mL). All ether layers were taken together and washed with water (100 mL). Ether layer was dried over anhydrous Na_2SO_4, the solvent was stripped off and then vacuum dried give III [8.2 g, yield=80.94%, %, $[\alpha]=+25.7^0$ (c=0.5, methanol), appearance: dark yellowish brown, viscous].

IR(KBr)$\upsilon_{cm^{-1}}$:1740.17cm^{-1}(-COOCH$_3$),1377.55cm^{-1} and 1368.73cm^{-1}(-O-C(CH$_3$)$_2$-O-).

^{1}HNMR: 3.66ppm (s,3H,-COOCH$_3$), 3.64ppm (t,J=5.46,2H,-CH$_2$-OH), 3.60ppm (bs,2H,-CH(O-)-CH(O-)-), 2.30ppm (t,J=7.44,2H,-CH$_2$COOCH$_3$), 1.37ppm (s,6H,-C(CH$_3$)$_2$-), 1.50ppm, 1.31ppm (s,22H,-CH$_2$-).

(+)*threo*-1,7(R),8(R),16-tetrahydroxyhexadecane-7(R),8(R)-acetonide (IV): A dry three neck round bottom flask, fitted with condenser, calcium chloride guard tube, and septum was cooled to 0-5^{0}C. LAH (1.82g, 0.048M) solution was taken in this under dry nitrogen. To this dry THF (50 mL) was added using a syringe. A solution of (+)*threo*-methyl 9(R),10(R),16 trihydroxyhexadecanoate - 9(R),10(R)-acetonide, III (7.0g, 0.022M) in dry THF (50 mL) was then added to the reaction mixture over a period of 30 minutes at 0-5^{0}C. The reaction was complete in 5hours. To this water (25 mL) was added slowly and cautiously, then the reaction mixture temperature was allowed to raise to room temperature (26^{0}C). The reaction mixture was filtered and THF was evaporated. The aqueous layer was further diluted with water (25 mL) and extracted with ether (3 × 50mL). All ether layers were collected and then dried over anhydrous Na_2SO_4. The ether was then evaporated and vacuum dried to give IV [4.1 g, yield=63.56%, $[\alpha]=+24.9^0$ (c=0.5, methanol), appearance: light yellow].

IR(KBr)υ_{cm-1}: Disappearance of peak at 1740.17cm^{-1} (-COOCH_3), 3424.38cm^{-1} CH_2-OH),1380.38cm^{-1}and1370cm^{-1} (-O-C(CH_3)$_2$-O-),

^{1}HNMR: 3.64ppm (t,J=5.46,4H,-CH_2-OH), 3.60ppm (bs,2H,-CH(O-)-CH(O-)), 1.37ppm (s,6H,-C(CH_3)$_2$-), 1.50ppm,1.31ppm (s,24H,-CH_2-).

(+)-threo-1,16-dibenzyloxy-7(R),8(R)- dihydroxyhexadecane (VI): In a three necked dry round bottom flask fitted with condenser, sodium hydride(55%, 1.22g, 0.028M) was taken. dry THF (10mL) was added under nitrogen and then stirred for 10 minutes. The reaction mixture was then allowed to stand for 5 minutes. The upper THF layer was removed by means of syringe. Same washing procedure was repeated to remove oil coating of sodium hydride. A solution of (+)*threo*-1,7(R),8(R),16-tetrahydroxyhexadecane-7(R),8(R)-acetonide, IV (4g, 0.012M) in dry THF (10 mL) was then added and reaction mixture was refluxed for 3 hours. It was then cooled to room temperature and to this benzyl chloride (3.18g, 0.0252M) in dry THF (10 mL) was added. The rection mixture was further refluxed for 5 hours, and then cooled to room temperature. Excess sodium hydride was quenched with slow additon of water (25 mL), this was then stirred for 15minutes. THF in reaction mixture was evaporated. Reaction mixture was diluted with water (50 mL) and extracted ether (3 × 50 mL). The ether layer was washed with water, dried over anhydrous Na_2SO_4 and then evaporated. The residue obtained was vacuum dried to give V [3.8 g, yield=95%, appearance: dark brown. The product was then purified by means of column chromatography, the material (3.5 g) was loaded on 60-120mesh size silica gel (35 g) in hexane. Hexane was used as the eluent and the polarity of the eluent was

successively increased with diethyl ether. The **1,16-Dibenzyloxy-7,8-dihydroxyhexadecane-7,8-acetonide(V)** was eluted with 2% ether in hexane [2.5 g, yield=4.45%, $[\alpha]=+25.6^0$ (c=0.5, methanol), appearance: pale yellow liquid].

IR(KBr)υ_{cm-1}:No peak was observed at 3368.08cm^{-1} (CH_2-OH), 1370cm^{-1}and1366.57cm^{-1} (-O-C(CH_3)$_2$-O-),

^{1}HNMR: 7.32ppm (s,10H,-CH_2-C_6H_5), 4.49ppm (s,4H,-O-CH_2-C_6H_5), 3.45ppm (t,J=6.5,4H,-CH_2-O-CH_2-C_6H_5), 3.57ppm (bs,2H,-CH(O-)-CH(O-)-), 1.37ppm (S,6H,-C(CH_3)$_2$-), 1.50ppm and 1.31ppm (s,24H,-CH_2-),

C,H.analysis:C=77.60%,H=9.87%,O=12.53%(calculated for $C_{33}H_{50}O_4$),

C=77.4%,H=9.8%,O=12.8% (found).

V was taken in THF (25 mL) and to this 2N Hcl (25 mL) was added and the reaction mixture was stirred at 60^{0}C for 2 hours, this was then cooled to room temperature, the THF was evaporated, and the reaction mixture was further diluted with water (25 mL). This was then extracted thrice with ethyl acetate (3 × 50 mL). The ethyl acetate layer was washed with water till neutral pH. Ethyl acetate layer was dried over anhydrous Na_2SO_4. Then ethyl acetate was evaporated, solid obtained was crystallized from hexane (25 mL) to give VI [1.45 g, yield=64.44%, $[\alpha]=+26.3^0$ (c=0.5, methanol), appearance: white solid, M.P.:63-64^{0}C].

I.R.(KBr)υ_{cm-1}: appearance of peak at 3419.25cm^{-1} (CH_2OH), and disappearance of doublet at 1370cm^{-1} and 1366.26cm^{-1} (-O-C(CH_3)$_2$-O-),

^{1}HNMR: 7.32ppm (s,10H,-CH_2-C_6H_5), 4.48ppm (s,4H,-O-CH_2-C_6H_5), 3.45ppm

(t,J=6.5,4H,-C<u>H</u>$_2$-O-CH$_2$-C$_6$H$_5$), 3.35ppm (bs,2H,-C<u>H</u>(OH)-C<u>H</u>(OH)-), 1.58ppm and 1.301ppm (s,24H,-C<u>H</u>$_2$-),

^{13}CNMR:128.69ppm (-CH$_2$-<u>C</u>$_6$H$_5$), 73.8ppm (-O-<u>C</u>H$_2$-C$_6$H$_5$), 75.2ppm (-<u>C</u>H(OH)-<u>C</u>H(OH)-), 71.4ppm (-<u>C</u>H$_2$-O-CH$_2$-), 26.9-33.8ppm(-<u>C</u>H$_2$-).

C,H analysis:C=76.55%,H=9.85%,O=13.60% (calculated for $C_{30}H_{46}O_4$), C=76.5%,H=9.7%,O=13.8% (found).

Preparation of reagent from Lithium aluminium hydride, (+)-threo-1,16-dibenzyloxy,7(R),8(R)-dihydroxy hexadecane and alcohol and reduction of alkyl phenyl ketones.

Typical procedure for reduction of acetophenone. To a solution of LAH (4 mmol) in THF (5 mL), was added a solution of (+)*threo*-1,16-dibenzyloxy,7(R),8(R)-dihydroxy hexadecane (1.9 g, 4.2 mmol) in dry THF (5 mL) and primary alcohol (4 mmol) at 0^{0}C. The reaction mixture was then refluxed for 1.5Hours, cooled to -78^{0}C, and a solution of acetophenone (120 mg, 1 mmol) in THF (5 mL) was added at once. The progress of the reaction was monitored using GLC (Column: 5%DEGS 9ft, 120^{0}C, isothermal, 25min). The temperature was maintained at -78^{0}C for 9hours, water was added causitiously, the reaction temperature was then raised to room temperature, and stirred for 15 minutes. THF was distilled off, water (10 mL) was added, filtered and extracted with hexane (1 × 10 mL). The combined hexane layer was cooled to 0^{0}C and chiral auxiliary separated was recovered by filtration. The hexane layer was dried over anhydrous Na_2SO_4, concentrated under vaccum to give phenylmethyl carbinol (79

mg, yield = 64.75%). In a similar manner other ketones were reduced. Chiral auxiliary recovered was crystalised once from hexane to give pure (+)-threo-1,16-dibenzyloxy-7(R),8(R)-dihydroxy hexadecane [1.78 g, yield=93.6 %, [α] = +25.1 (c=0.5%, methanol)].

Conclusion :

A reagent derived by complexation of LAH with (+)*threo*-1,16-dibenzyloxy,7(R),8(R)-dihydroxy hexadecane (synthesized from (+)*threo*-aleuritic acid) when used along with a long chain alcohol (C12-16) reduced prochiral ketones with moderate (68-70%ee) enantioselectivity. The moderate enantioselectivity can be attributed to non-single hydride species available for the reduction of prochiral ketones. The role of length of carbon chain as an additive alcohol for anchoring one of the hydrogen of complex formed of LAH with (+)*threo*-1,16-dibenzyloxy,7(R),8(R)-dihydroxy hexadecane was important for increasing enantioselectivity. Mechanism for predominant formation of R-isomer based on transition state and the difference between the groups attached to carbonyl group of ketone was postulated.

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