Pergamon

Tetrahedron 54 (1998) 3929–3934

TETRAHEDRON

Stereoselective Total Syntheses of 9(S)- and 9(R)-HETE

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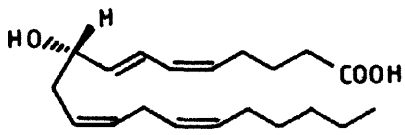
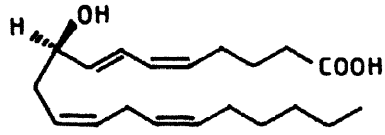
Received 31 December 1997; accepted 5 February 1998

Abstract : A simple and efficient stereoselective total synthesis of methyl 9(S)-and 9(R)-hydroxy -5(Z), 7(E), 11(Z), 14(Z)-eicosatetraenoates using base induced opening of chiral 2,3-epoxy chlorides is described.

During our continuing studies[1-8] on the synthesis of lipoxygenase derived metabolites of arachidonic acid, we turned our attention towards 9-hydroxy eicosatetraenoic acid (9-HETE). Previously, this compound has not been the subject of many investigations (it has been shown to possess chemotactic activity[9]) and only few syntheses have been reported.[10-12] LTB_4 and various monohydroxy eicosatetraenoic acids (5-HETE, 9-HETE, 11-HETE, 12-HETE and 15-HETE) have been isolated and identified from incubation of chopped rat brain tissue with ionophore A 23187.[13] Among the six possible HETEs described in mammalian systems, the 5-, 11-, 12- and 15-HETEs are all well established natural products, whose biological activities are being investigated with great intensity.[14-16] Little is known about the 8- and 9-HETEs. The non-availability of these compounds in substantial quantities has prevented the complete analysis. In the interest of fully evaluating the biological properties of 9-HETE, it was desirable to obtain adequate supplies of both enantiomers. In view of the importance of these compounds and also in order to test the generality of our synthetic method, we have synthesized 9(S)- and 9(R)- HETEs in a stereodefined manner, the results being presented herein.



9(S) - HETE



9(R) - HETE

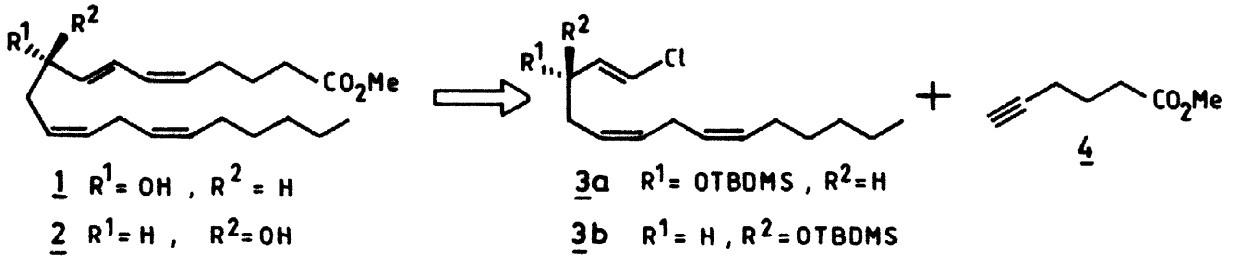
The general strategy for the synthesis of **1** and **2** is formulated, based on the retrosynthetic analysis as shown in **scheme 1**. A Pd^0-Cu^I mediated coupling[17,18] of a terminal acetylene **4** with chlorovinyl alcohol **3**

IICT Communication No. 3901

0040-4020/98/$19.00
PII: S0040-4020(98)00119-7

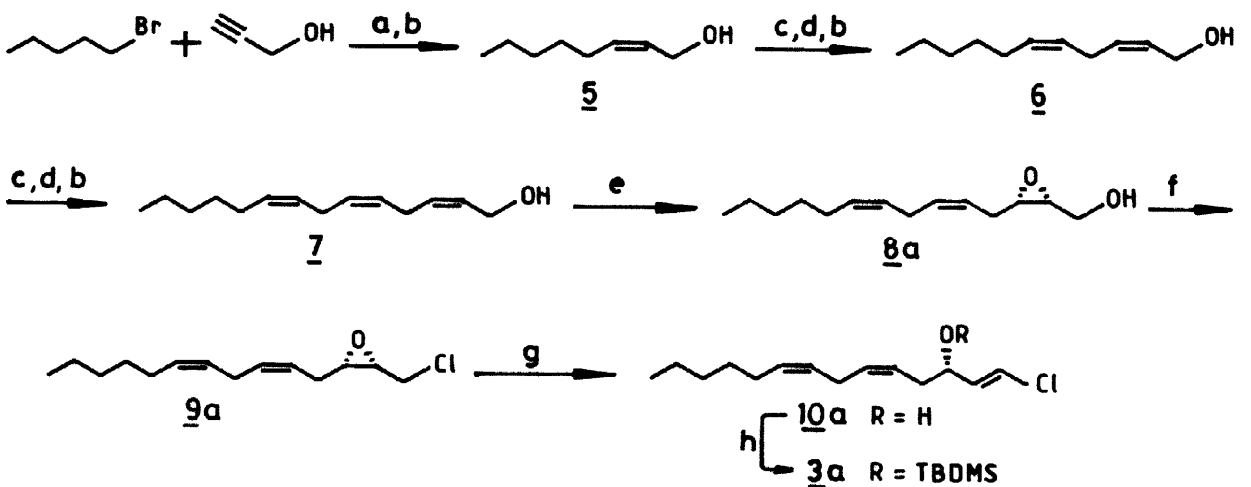
should give the enyne intermediate which on subsequent transformations would afford the desired products **1** and **2** respectively.

Scheme 1



Accordingly an efficient approach for the synthesis of intermediate **3** was developed as depicted in **scheme 2**. Alkylation of propargyl alcohol with 1-bromo pentane followed by partial hydrogenation using $Ni(OAc)_2$, $NaBH_4$, ethylene diamine in EtOH[19] gave the enol **5** in 75% yield. Bromination of **5** and repeated treatment of alkylation and reduction with $Ni(OAc)_2$, $NaBH_4$, ethylene diamine in EtOH resulted in the dienol[20] **6** in 75% yield.

Scheme 2



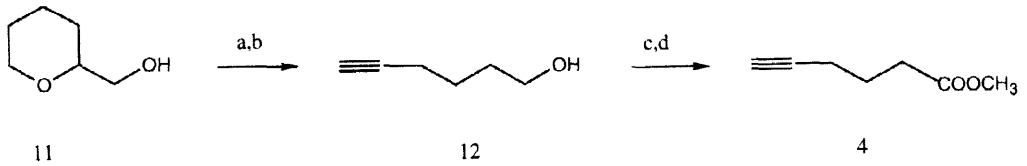
Reagents : a) $LiNH_2$, liq. NH_3; b) $Ni(OAc)_2$, $NaBH_4$, $(CH_2NH_2)_2$, EtOH; c) PBr_3, Et_2O; d) EtMgBr, propargyl alcohol, THF; e) (-) DIPT, TIP, TBHP, 4A°mol. sieves; f) Ph_3P, CCl_4, $NaHCO_3$; g) $LiNH_2$ in liq. NH_3, -33°C; h) TBDMSCl, imidazole, CH_2Cl_2.

The trienol **7** obtained by adopting the same methodology used for the moiety **6**, was subjected to Sharpless epoxidation[21] with (-) DIPT to afford the corresponding epoxide **8a** selectively in 90% yield. Epoxy alcohol **8a** was converted to the corresponding epoxy chloride **9a** employing PPh_3, $NaHCO_3$ in refluxing CCl_4. The epoxide **9a** was opened, using our well established synthetic strategy,[6] by treatment with 1 equivalent of freshly prepared $LiNH_2$ in liq. NH_3 at -33°C and obtained exclusively trans vinyl chloride[22] **10a** in 87% yield. The compound **10a** on treatment with TBDMSCl in presence of imidazole furnished the intermediate **3a** in 95% yield.

The intermediate **4** was synthesized by the reported method[23] as shown in **Scheme 3**. Tetrahydropyranyl chloride, obtained from tetrahydropyranyl alcohol, on treatment with $NaNH_2$ in liq. NH_3 at -33°C afforded 5-

hexynol **12** which on subsequent Jones' oxidation[24] and esterification gave **4** in quantitative yields.

Scheme 3

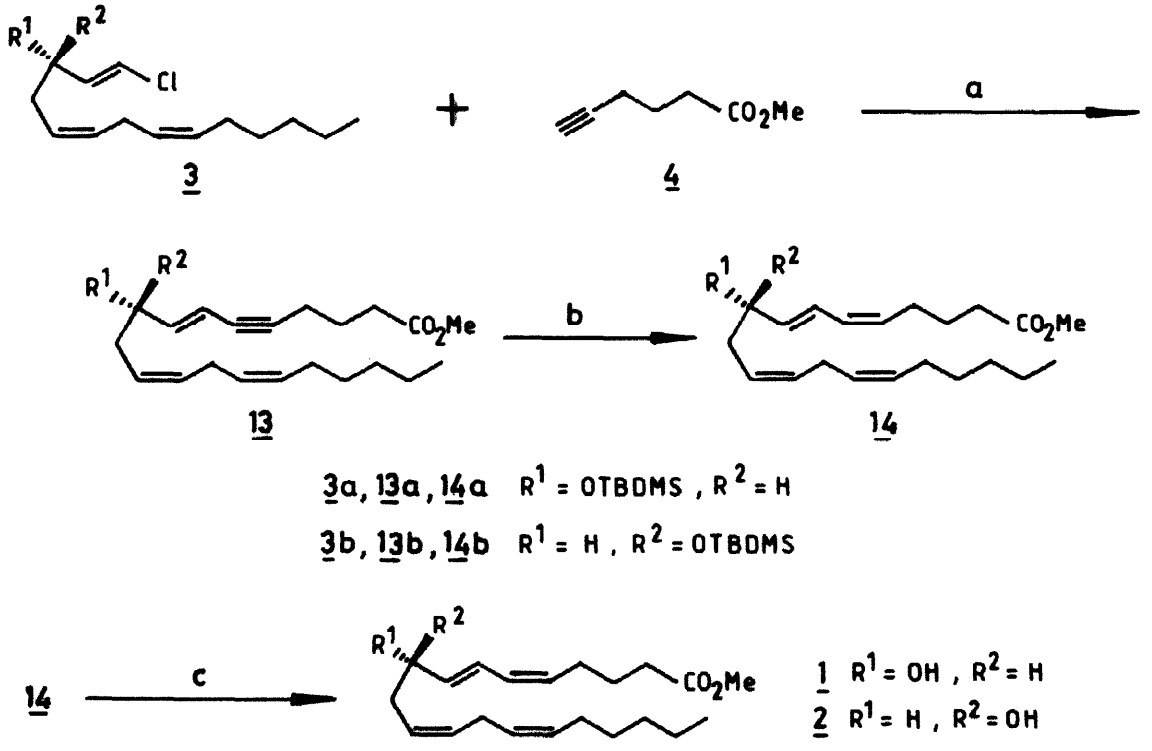


11 12 4

Reagents : a) $SOCl_2$, Pyr; b) Na, liq. NH_3; c) CrO_3, H_2SO_4, H_2O, Acetone, ; d) $(CH_3)_2SO_4$, K_2CO_3, Acetone, reflux.

The $PdCl_2(PhCN)_2$, CuI catalysed coupling reaction[17] of **4** with retron **3a** in the presence of 20 equivalents of piperidine in THF resulted in the formation of compound **13a** in 92% yield. The target compound **1** was elaborated as shown in **scheme 4** from **13a** employing series of reactions viz, initial selective reduction of triple bond using Lindlar catalyst and deprotection of TBDMS group using 1% HCl in MeOH. $[\alpha]_D$ -7.2 (c 2.0, $CHCl_3$) lit. - 7.1 (c 2.05, $CHCl_3$) and the spectral data were consistent with the reported values.[11]

Scheme 4



Reagent : (a) $PdCl_2(PhCN)_2$, CuI, Piperidine, THF, RT; (b) Pd-$CaCO_3$, quinoline, H_2, EtOH; (c) 1% HCl in MeOH.

The enantiomer 9(R)-HETE was prepared selectively in a similar fashion by using (+) DIPT instead of (–) DIPT, in the Sharpless epoxidation step.

Thus, in conclusion it has been amply demonstrated, in the synthesis of methyl esters of 9(S) and 9(R)-hydroxy-5(Z), 7(E), 11(Z), 14(Z)-eicosatetraenoic acids, the usefulness of the chiral building blocks prepared by our methodology; i.e., the base induced opening of epoxy chlorides. The synthetic strategy reported herein opens new avenues for making related metabolites for biological evaluation.

EXPERIMENTAL SECTION

IR spectra were recorded as neat film on Perkin-Elmer 683 or 1310 spctrometers. ^{1}H NMR spectra were recorded by Gemini spectrometer 200 MHz with $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded on either Micro Mass 7070 H or Finnigan Mat 1020 B mass spectrometer operating at 70 ev and optical rotations were recorded by Jasco Dip-370 polarimeter. All the starting materials were prepared by the standard procedures.

Synthesis of 9(S)-HETE methyl ester:

(2S-cis) (3Z, 6Z-undeca-dienyl) oxirane methanol (8a)

To a stirred and cooled (-20°C) suspension of activated, powdered 4A^0 molecular sieves (2g) in CH_2Cl_2 (50 ml) under N_2 atmosphere (–) DIPT (0.11 g, 0.47 mmol), Ti $(OiPr)_4$ (0.136 g, 0.48 mmol), and TBHP , 7.5 M in toluene (1.29g, 14.42 mmol) were added sequentially. After 20 mins, the allyl alcohol **7** (2.0 g, 9.61 mmol) in CH_2Cl_2 (10ml) was added to the reaction mixture over a period of 20 minutes and was held at -20^0 C for 4 h. The reaction mixture was allowed to warm to 0^0 C and poured into a freshly prepared and cooled (0° C) saturated solution (10 ml) of 1:1 ferrous sulfate and tartaric acid in deionised water. The two phase mixture was stirred for 25-30 mins, the aqueous phase separated and extracted with ether. The combined organic phases were treated with a precooled (0°C) solution of 30% NaOH. The two phase mixture was then stirred for 1 h at room temperature and aqueous layer separated. It was treated with ether, combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford epoxy alcohol **8a** (1.93 g) in 90% yield as liquid product after column chromatography (20% ethyl acetate - hexane). ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.9 (t, 3H, J=8.08 Hz); 1.15-1.45 (m, 6H); 1.78-2.1 (m, 3H); 2.12-2.55 (m, 2H); 2.63-2.83 (m, 2H); 2.95-3.18 (m, 2H); 3.58-3.92 (m, 2H); 5.16-5.7 (m, 4H); ^{13}C NMR ($CDCl_3$, 50MHz) : δ 130, 127, 125, 124, 61, 57, 32, 31, 29, 28, 27, 26, 23, 14; IR (Neat) : 3430, 2925, 1675, 1260 cm^{-1}, MS: m/z; 224(M^+); $[\alpha]_D^{27}$ -12.36 (c 1.1, $CHCl_3$).

(2S-cis)-(3Z, 6Z-undeca-dienyl) oxirane methyl chloride (9a)

A stirred mixture of epoxy alcohol **8a** (1.2 g, 5.35 mmol); PPh_3 (1.4 g, 5.35 mmol) and $NaHCO_3$ (1.2 g) in CCl_4 (20ml) was refluxed for 3 h under N_2 atmosphere. Removal of CCl_4 under asperator pressure followed by purification using column chromatography (SiO_2, pet ether) afforded the epoxy chloride **9a** (1.28 g) in 99% yield. ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.85 (m, 3H); 1.1-1.5 (m, 6H); 1.87-2.1 (m, 2H); 2.12-2.5 (m, 2H); 2.6-2.8 (m, 2H); 2.9-3.1 (m, 1H); 3.1-3.25 (m, 1H); 3.33-3.5 (m, 1H); 3.57-3.75 (m, 1H); 5.17-5.63 (m, 4H); IR (Neat) : 1460, 1260 cm^{-1}; MS : m/z 242, 244; $[\alpha]_D^{25}$ -6.18 (c 1.3, $CHCl_3$).

(1E, 3S, 5Z, 8Z)-1-Chloro-1, 5, 8-tetradecatrien-3-ol (10a)

To a freshly prepared suspension of $LiNH_2$ in liq. NH_3 [prepared from 0.049 g. atom lithium in liquid NH_3 (5 ml)] was added epoxy chloride **9a** (0.5 g, 2.06 mmol) in THF (1 ml) at -33°C. Reaction mixture was stirred for 15 mins. and ammonia was allowed to evaporate, after quenching it by solid NH_4Cl. Residue was treated with water, extracted with ether. The organic layer was washed with water, brine, dried (Na_2SO_4), evaporated and purified by column chromatography (silica gel, 2% ethyl acetate- pet ether) to give **10 a** (0.41 g) in 87% yield. ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.85 (m, 3H); 1.1-1.42 (m, 6H); 1.6-1.8 (s, 1H); 1.84-2.08 (m, 2H); 2.15-2.38 (m, 2H); 2.6-2.8 (m, 2H); 4.0-4.18 (m, 1H); 5.12-5.6 (m, 4H); 5.8-5.98 (dd, 1H, J=6, 14 Hz); 6.17 (d, 1H, J=14 Hz); IR (Neat) : 3340, 2930, 1600 cm^{-1} ; MS : m/z 242, 207; $[\alpha]_D^{25}$ -3.13 (c 0.6, $CHCl_3$).

(1E, 3S, 5Z, 8Z)-1-Chloro-3-t-butyl dimethyl silyloxy-1,5,8-tetradecatriene (3a)

To a mixture of trans vinyl chloro alcohol **10a** (0.5 g, 2.06 mmol) and imidazole (0.28 g, 4.12 mmol) in dry CH_2Cl_2(10ml) was added t-butyl dimethyl silyl chloride (0.372 g, 2.47 mmol). The mixture was then refluxed for 2h, diluted with ether, washed with saturated aq NaCl (4x10 ml) and dried over Na_2SO_4. Solvent was removed in *vacuo* and the residue was purified by column chromatography on silica gel (pet ether) to afford the pure silyl ether as the sole product in 95% yield (0.698 g). ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (s, 6H); 0.82 (m, 12H); 1.1-1.4 (m, 6H); 1.85-2.05 (m, 2H); 2.07-2.28 (m, 2H); 2.58-2.75 (m, 2H); 4.0-4.15 (m, 1H); 5.13-5.48 (m, 4H); 5.75-5.91 (dd, 1H, J=6.8, 13.63 Hz); 6.05 (d, 1H, J=13.63 Hz); ^{13}C NMR ($CDCl_3$, 50MHz) : δ 136, 132, 131, 127, 126, 118, 72, 42, 36, 32, 31, 30, 27, 26, 23, 14, -4; IR (Neat) : 2930, 1600 cm^{-1} ; MS : m/z 356; $[\alpha]_D^{27}$ +2.37 (c 2.3, $CHCl_3$).

Methyl (7E, 9S, 11Z, 14Z)-9-t-butyl dimethyl silyloxy eicosa-7,11,14-trien-5-yn-oate (13a)

To a stirred mixture of **3a** (0.1 g, 0.28 mmol) and $PdCl_2$ (Ph CN)$_2$ (0.010 g, 0.028 mmol) in dry THF (2 ml), 20 equivalents of piperidine (0.476 g, 5.606 mmol) was added followed by acetylene ester (0.063 g, 0.50 mmol). To this mixture CuI (0.005 g, 0.028 mmol) was added and stirred for 6 h under nitrogen atmosphere. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with ether. The combined ethereal layer was washed with water, brine, dried over Na_2SO_4, concentrated and purified by column chromatography (silica gel, 5% EtOAc in pet ether) to furnish pure **13a** (0.115 g) in 92% yield. ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.05 (s, 6H); 0.78-1.0 (m, 12H); 1.15-1.40 (m, 6H); 1.73-1.92 (m, 2H); 1.92-2.1 (m, 2H); 2.1-2.3 (m, 2H); 2.3-2.5 (m, 4H); 2.61-2.8 (m, 2H); 3.65 (s, 3H); 4.02-4.21 (m, 1H); 5.20-5.48 (m, 4H); 5.56 (d, 1H, J=14.89 Hz); 5.88-6.06 (dd, 1H, J=6.38 Hz, 14.89 Hz); ^{13}C NMR ($CDCl_3$, 50MHz) : δ 174, 145, 132, 131, 128, 126, 125, 109, 89, 80, 73, 52, 41, 36, 33, 31, 30, 29, 27, 26, 24, 22, 14, -4; IR (Neat) : 3460, 2930, 2250, 1730 cm^{-1}; MS : m/z 446; $[\alpha]_D^{27}$ +2.44 (c 1.5, $CHCl_3$).

Methyl-(5Z, 7E, 9S, 11Z, 14Z)-9-t-butyl dimethyl silyloxy-5,7,11,14-eicosatetraenoate (14a)

To the Lindlar catalyst (0.1 g) in absolute ethanol (5 ml) was added the acetylene **13a** (0.2 g, 0.448 mmol) under H_2 atmosphere. After 10 min of vigorous stirring, the reaction mixture was observed to absorb ~10 ml of H_2 and the stirring was stopped. Catalyst was filtered, and filtrate concentrated under reduced pressure to afford pure tetraolefin in 90% yield (0.18 g). ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.0-0.1 (m, 6H); 0.8-1.0 (m, 12H); 1.1-1.5 (m, 8H); 1.58-1.82 (m, 2H); 1.91-2.1 (m, 2H); 2.1-2.38 (m, 4H); 2.67-2.82 (m, 2H); 3.65 (s, 3H); 4.08-4.25 (m, 1H); 5.21-5.47 (m, 5H); 5.54-5.71 (dd, 1H, J=6.06, 16.16 Hz); 5.99 (t, 1H, J=12.12 Hz); 6.3-6.48 (dd, 1H, J=8.08, 12.12 Hz); IR (Neat) : 3460, 2930, 1730 cm^{-1}; MS : m/z 448; $[\alpha]_D^{24}$ +3.50 (c 0.85, $CHCl_3$).

Methyl (5Z, 7E, 9S, 11Z, 14Z)-9-hydroxy-5,7,11,14-eicosatetraenoate (1)

The target compound **1** was obtained by treating the ether **14a** (0.05 g, 0.11 mmol) with 2 ml of 1% HCl in MeOH at room temperature in 70% (0.026 g) yield. ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 0.89 (t, 3H, J=8.08 Hz); 1.12-1.48 (m, 6H); 1.48-1.8 (m, 3H); 1.90-2.25 (m, 4H); 2.33 (t, 4H, J=4.04 Hz); 2.63-2.82 (m, 2H); 3.62 (s, 3H); 4.06-4.23 (m, 1H); 5.25-5.55 (m, 5H); 5.71 (dd, 1H, J=6.06, 16.16 Hz); 6.0 (t, 1H, J=11.1 Hz); 6.3-6.48 (dd, 1H, J=11.5, 14.3 Hz); IR (Neat): 3340, 2930, 1730 cm^{-1}; MS : m/z 334, 316; $[\alpha]_D^{22}$ -7.2 (c 2.0, $CHCl_3$).

Synthesis of 9(R)-HETE methyl ester :
(2R-cis)-(3Z, 6Z-undecadienyl) oxirane methanol (8b)

Sharpless asymmetric epoxidation on **7** was carried out using (+) DIPT under identical conditions as for **8a**. ^{1}H NMR, IR and mass spectra for this compound are superimposable to those obtained for the enantiomer **8a**. $[\alpha]_D^{27}$ +12.36 (c 1.1, $CHCl_3$).

Taking **8b** as the starting material, the entire sequence of reactions have been repeated, as described for their **8a** series counterparts, to obtain compounds **9b**, **10b**, **3b**, **13b**, **14b** and finally the required (5Z, 7E, 9R, 11Z, 14Z)-9-hydroxy-5, 7, 11, 14-eicosatetraenoate **2**. Structure was established beyond doubt by obtaining superimposable ^{1}H NMR, IR and MS with their counterpart enantiomers. However, the absolute value of the $[\alpha]_D$ remained the same, with reversal in sign.

Acknowledgements

Two of the authors (L.R.M. Bhanu and D. Dutta) wish to thank CSIR-UGC (New Delhi) for financial assistance.

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