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A Stereoselective Synthesis of 8(R) and 8(S),11(R),12(S)-Trihydroxyeicosa-5(Z),9(E),14(Z)-Trienoic Acid from 2-Deoxy-D-Ribose

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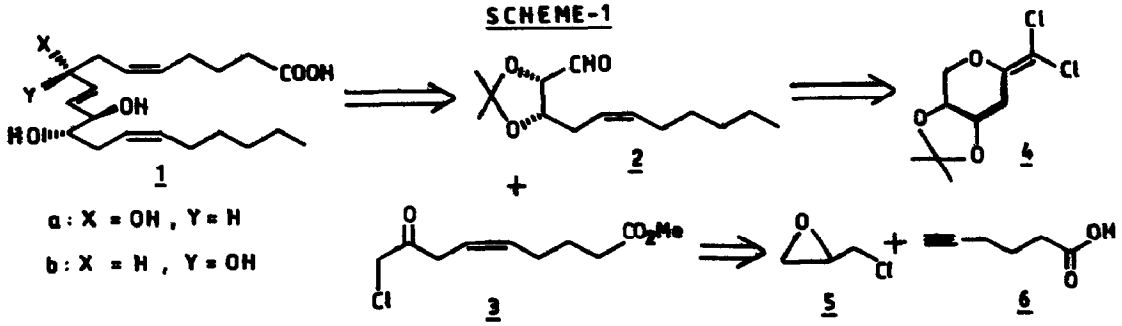
Abstract: A stereoselective synthesis of stereoisomers of the title compound from 2-deoxy-D-Ribose using reductive elimination protocol[1] as the key step is described.

Hepoxilins[2,3] are biologically potent epoxy alcohols derived from 12(S) HPETE via 12-lipoxygenation pathways and play[4] crucial role in haemostasis and several respiratory disorders. Recent findings have also shown that they have insulin secretagogue activity[5] and have possible role as second messengers for presynaptic inhibitors of Aplysia sensory cells[6] which brought these compounds to the fore. Scarce availability of hepoxilins obscured the exact mode of their action in pharmacological profile. Trioxilin A_3, formed from Hepoxilin A_3 via the same 12-lipoxygenase pathway involving epoxide hydratase enzyme, has been identified[7] as a mixture of 8R/S,11R,12S-trihydroxyeicosa-5Z,9E,14Z-trienoic acid. To extend the scope of further exploration of the physiological importance of this novel class of eicosanoids and also to study the bioefficacy of hepoxilins and trioxilin A_3 in particular, we herein report a practical and stereoselective total synthesis of both 8R and 8S isomers of trioxilin A_3, from the chiral precursor 2-deoxy-D-ribose in which the C-3 and C-4 chiral centres are correlated to the 12S and 11R carbon centres of the target molecule.

The following retrosynthetic analysis (scheme 1) reveals the strategy.

SCHEME-1



The crucial E-olefinic system present at C-9 of 1 can be envisioned from the stereocontrolled Wittig olefination[8] of chiral carbinal 2 with the ylide of 3.

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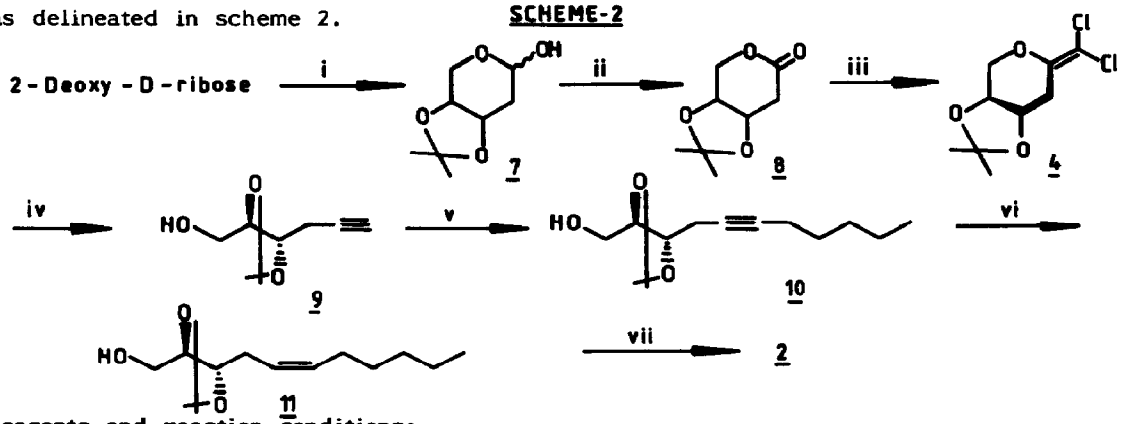
Further, the chiral retron 2 can be synthesized in high yields by the methodology recently developed by us[1] involving reductive elimination of the dichloromethylene compound 4. The chiral retron 2, was prepared from 2-deoxy-D-ribose in 7 steps as delineated in scheme 2.

SCHEME-2

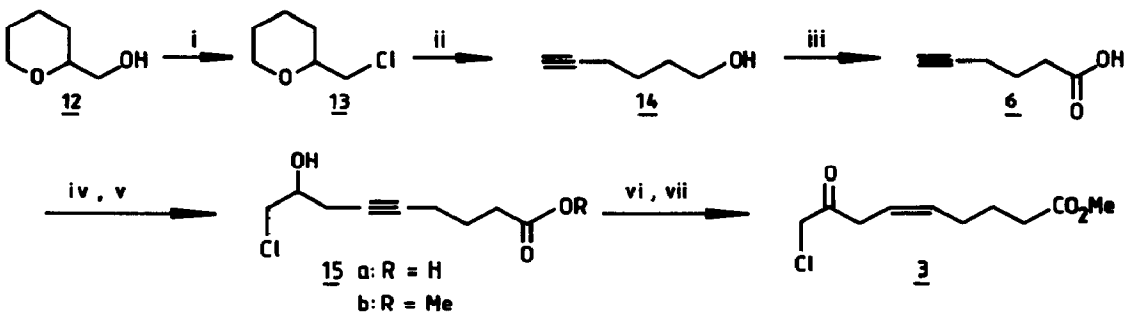


Reagents and reaction conditions:
(i)2-Methoxypropene,PPTS,EtOAc,rt,3h(ii)Br_2 -$CaCO_3$,Acetonitrile:H_2O(5:1),rt,24h(iii) PPh_3 ,CCl_4 ,THF reflux(iv)Li sand,THF,reflux,3h(v)n-BuLi,pentyl bromide,THF:HMPA (10:1),-78° to rt(vi)Pd-$CaCO_3$,H_2,EtOH,3h(vii)$(COCl)_2$,DMSO,TEA,DCM,-78°C.

Protection of the hydroxyl groups of 2-deoxy-D-ribose[9] with 2-methoxy propene under PPTS conditions led to rearranged product 7. Oxidation of lactal 7 to lactone 8 was achieved in 85% yields under Br_2-$CaCO_3$ conditions. Chapleur's[10] method of dichloromethylenation of 8 led to 4 in good yields. The crucial synthon 9 was obtained from 4 in 85-90% yields by following our reductive elimination process.[1,11] Alkylation of the lithium alkylide of 9 with amyl bromide followed by hydrogenation under Lindlar's conditions have the Z-olefinic alcohol 11 in overall 80% yield. Swern oxidation of 11 afforded the intermediate 2 in 80% yield.

The retron 3 was prepared efficiently by a new route from the commercially available epichlorohydrin 5 and 5-hexynoic acid 6, employing Yamaguchi's[12] method of oxirane opening with alkynyl boranes as shown in scheme 3.

SCHEME-3

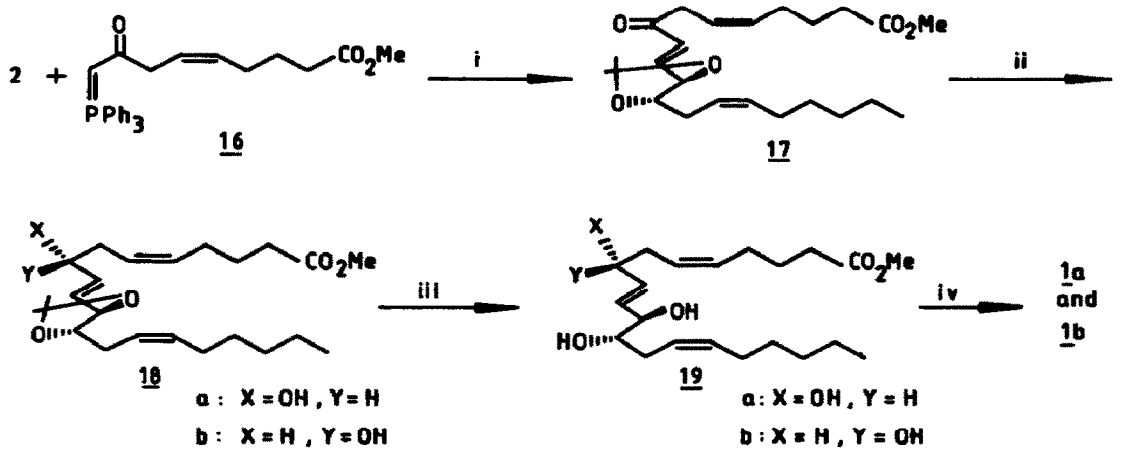


Reagents and reaction conditions:
(i)$SOCl_2$,Pyridine,rt,10h(ii)$NaNH_2$,liq.NH_3 ,-78°,THF(iii)Jones' reagent,acetone,0°(iv) n-BuLi,BF_3 $(OEt)_2$,epichlorohydrin,-78°,THF(v)CH_2N_2 ,ether(vi)Jones' reagent,acetone, 0°C.

Hexynoic acid 6 was prepared in substantial yields by base induced double elimination of tetrahydropyranylchloride 13 leading to acetylenic alcohol 14 followed by Jones' oxidation. Treatment of 6 with two equivalents of n-BuLi at -78°C followed by the addition of 5 led uneventfully to 15a in 65% yields. Chloroketone 3 was prepared from 15a via a sequence of reaction involving conversion of acid to methyl ester 15b, hydrogenation over Lindlar's catalyst and then Jones' oxidation in overall 70% yield.[13]

The final conversion to the target molecule 1 through the stereocontrolled Wittig olefination[8] of 2 with the stable ylide 16 prepared from retron 3 is depicted in scheme 4.

SCHEME-4



Reagents and reaction conditions:
(i)Benzene,rt,10h(ii)$NaBH_4$,methanol,0°,10min(iii)6N HCl,THF,rt,6h(iv)LiOH,MeOH-H_2O(2:1),28°C,10h.

Chloroketone 3 was converted to its corresponding triphenyl phosphonium salt on treatment with one equivalent of Ph_3P in $CHCl_3$ followed by base treatment which gave ylide 16. Aldehyde 2 was added to ylide in dry benzene and stirred at room temperature to result in the E-olefinic product 17 in 80% yield, well confirmed by NMR spectrum.[14] Reduction of 17 with $NaBH_4$ in methanol at 0° gave diastereomeric mixture 18 (80% yield) in the ratio of 3:2 corresponding to 18a and 18b respectively, separable by flash column chromatography. Acetonide deprotection of 18a and 18b gave the triol esters 19a and 19b respectively, which were concurrent with the spectral data and specific rotations of the reported values,[15] 19a $[\alpha]_D$ -8.122°(C 0.5 CCl_4) (lit -8.0°;C 0.65 CCl_4), 19b $[\alpha]_D$ +3.066°(C 1.2 CCl_4)(lit +2.8°;C 0.58 CCl_4). Further saponification of 19a and 19b resulted in the title compounds 1a and 1b.

Thus, the synthesis of title compounds have been demonstrated by a concise and convenient route involving the reductive elimination reaction developed by us as a key step.

References and Notes

1. Yadav, J.S.; Prahlad, V. and Chander, M.C. J.Chem.Soc.,Chem.Commu. **1993**, 317-318.
2. (a) Walker, I.C.; Jones, R.L. and Wilson, N.H. Prostaglandins **1979**, 18, 173.
   (b) Pace-Asciak, C.R.; Mizumo, K. and Yamamoto, S. Biochim Biophys Acta, **1982**, 712, 142.
3. Corey, E.J.; Kang, J.; Laguzza, B.C. and Jones, R.L. Tetrahedron Lett. **1983**, 24, 4913.
4. Samuelsson, B.; Dahlem, S.E.; Lindgren, J.A.; Rouzer, C.A.; Serham, C.N. Science **1987**, 237, 1171.
5. Pace-Asciak, C.R.; Martin, J.M. and Corey, E.J.; Prog Lipid Res. **1986**, 25, 625.
6. Piomelli, D.; Feinmark, S.J. and Schwartz, J.H. Society for Neuroscience, 17th Annual Meeting, New Orleans, Louisiana, November 16-21, **1987**. Abstract No.169.11, p 598.
7. Pace-Asciak, C.R.; Laneuville, O.; Su, W-g.; Corey, E.J.; Gurevich, N.; Wu, P. and Carlen, P.L. Proc. Natl. Acad. Sci. USA, **1990**, 87, 3097-3041.
8. Corey, E.J. and Su, W-g. Tetrahedron Lett. **1984**, 25, 5119-5122.
9. Corey, E.J.; Marfat, A.; Goto, G. and Brias, F. J.Am.Chem.Soc. **1980**, 102, 7984-7985.
10. Lakhrissi, M. and Chapleur, Y. Syn.Lett. **1991**, 583.
11. Spectral data for **9**: 200 MHz ^{1}H NMR ($CDCl_3$): δ 4.40-4.20 (m,2H), 3.85-3.65 (dd,2H), J=6.13,4.08 Hz, 2.55-2.45 (m,2H), 2.05 (t,1H,J=2.0 Hz), 1.45 (s,3H), 1.35 (s,3H); $[\alpha]_D$ +16.4°(C 0.5,$CHCl_3$).
12. Yamaguchi, M. and Ichiro, H. Tetrahedron Lett. **1983**, 24, 391-394.
13. Spectral data for **3**: 200 MHz ^{1}H NMR ($CDCl_3$): δ 5.65-5.50 (m,2H), 4.1 (s,2H), 3.65 (s,3H), 3.35 (d,2H,J=6.4 Hz), 2.29 (t,2H,J=7.5 Hz), 2.05 (q,2H,J=6.3,9.6 Hz), 1.75-1.60 (m,2H).
14. Spectral data for **17**: 200 MHz ^{1}H NMR ($CDCl_3$): δ 6.65 (dd,1H,J=16.3,5.8 Hz), 6.4 (d,1H,16.3 Hz), 5.6-5.4 (m,4H), 4.7 (dd,1H,J=6.3,5.4 Hz), 4.3-4.2 (dt,1H, J=6.3,13.0 Hz), 3.7 (s,3H), 3.3 (d,2H,J=6.3 Hz), 2.4-2.0 (m,8H), 1.8-1.4 (m,8H), 1.38 (s,3H), 1.37 (s,3H), 0.9 (t,3H,J=6.3 Hz); $[\alpha]_D$ -3.9° (C 0.9, $CHCl_3$).
15. Lumin, S.; Falck, J.R.; Capdevilla, J. and Karara, A. Tetrahedron Lett. **1992**, 33, 2091.

+ All the new compounds gave expected spectral data including HRMS.

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