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A PRACTICAL METHOD FOR MULTIGRAM SCALE SYNTHESIS OF (+)-METHYL 5(S),6(R)-EPOXY-6-FORMYLHEXANOATE AND 2(R),3(S)-EPOXYOCTANAL, KEY INTERMEDIATES FOR SYNTHESIS OF LEUKOTRIENES A_4

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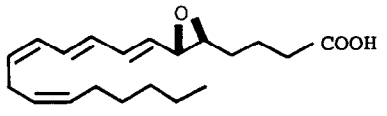
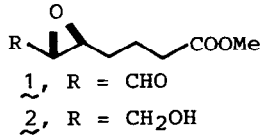
Summary: A practical method for multigram scale synthesis of (+)-methyl 5(S),6(R)-epoxy-6-formylhexanoate (1) and 2(R),3(S)-epoxyoctanal (13), key intermediates for synthesis of leukotrienes A_4, starting with (R)-glyceraldehyde acetonide (3) is described.

The preparation of (+)-methyl 5(S),6(R)-epoxy-6-formylhexanoate (1), which is the key intermediate in synthesis of natural leukotriene A_4 (LTA_4), has attracted much interest in recent years.[1] A chiral pool approach has been shown to be an effective and practical method for preparation of 1.[3] Thus, 1 was synthesized starting with (-)-D-ribose,[2] (+)-2-deoxy-D-ribose,[3] (-)-D-araboascorbic acid,[4] or (+)-D-glucose.[4] The asymmetric epoxidation of

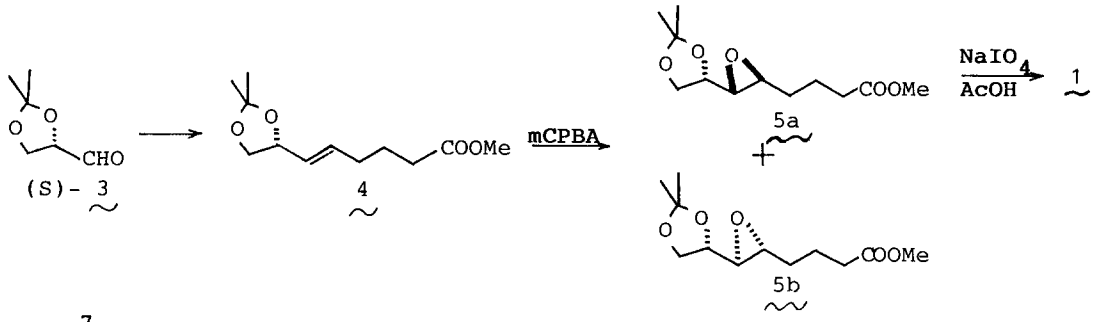


leukotriene A_4



1, R = CHO
2, R = CH_2OH

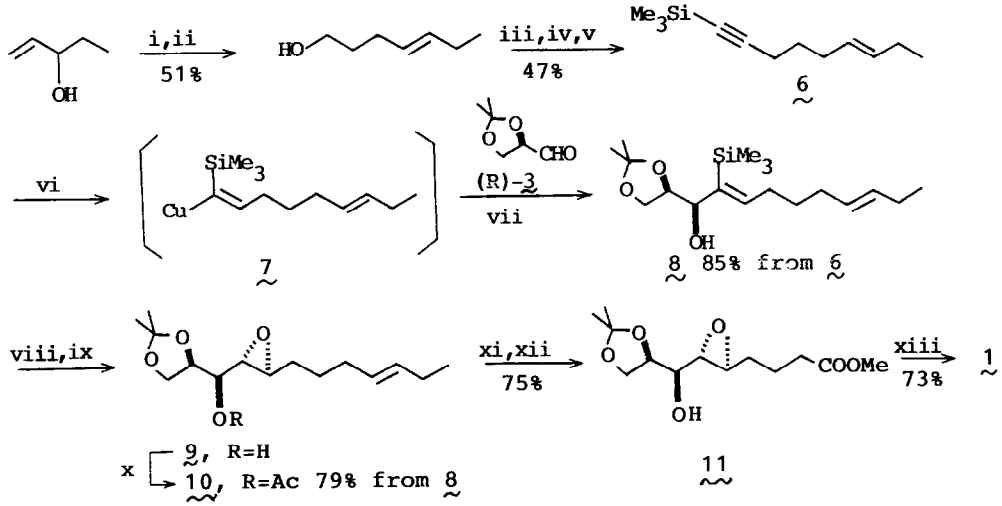
achiral allylic alcohols using the Sharpless process is another practical approach to 1.[5] These syntheses involve the oxidation of the epoxy alcohol 2 to 1 using Collins reagent. This oxidation step, however, required more than 6 equiv of $CrO_3 \cdot 2C_5H_5N$ and the dimeric ester was produced as a by-product, thus, making isolation and purification process somewhat troublesome. So far only one report is available in which 1 is synthesized without passing through 2.[6] Thus, Rokach and his coworkers synthesized 1 by oxidative cleavage of 5a which was prepared by epoxidation of the olefinic ester 4 obtained from (S)-glyceraldehyde acetonide 3.[7] This epoxidation step, however, suffers from low diastereoselectivity of 2 : 1. Herein we report a highly selective method for large-scale preparation of 1 without passing through 2 starting with (R)-3[8] which is more readily available than



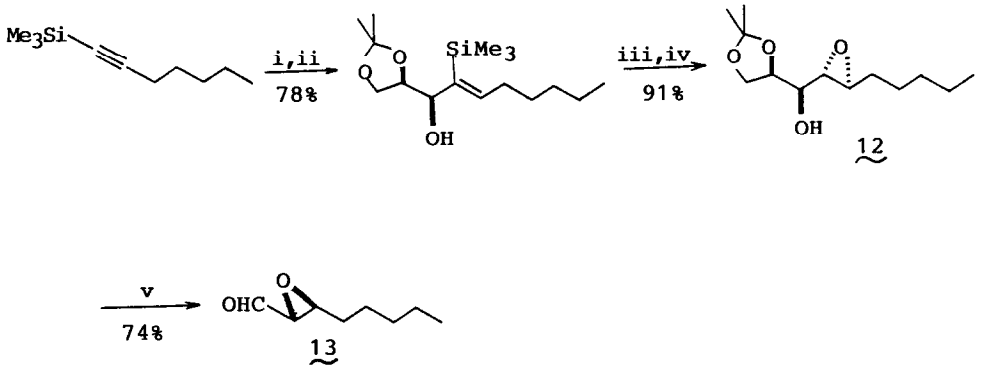
(S)-3.[7] The present method is based on the highly diastereoselective addition reaction of 3 with 1-trimethylsilylvinyl copper compounds[9] and the V^{5+}-catalyzed epoxidation of the resulting adducts with t-butylhydroperoxide (TBHP) which proceeds with near 100% diastereoselectivity.[10]

Our synthesis of 1 is detailed in Scheme 1. The acetylene 6 was prepared in large quantity in 24% overall yield from commercially available 1-penten-3-ol using a couple of operationally simple reactions. Hydromagnesiation[11] of 6 (4.0 g, 21 mmol) using Bu^iMgBr (18 mmol) and $(\eta\text{-}C_5H_5)_2TiCl_2$ (159 mg, 0.6 mmol) in Et_2O (26 ml), treatment with CuI (4.6 g, 24 mmol) in THF (100 ml) and Me_2S (13 ml) (-70 °C, 30 min) and then with (R)-3 (1.58 g, 12.1 mmol) (-70 °C, 30 min and then -70 °C→room temperature, 3 h) provided 8 (3.36 g, 85% based on (R)-3) with a high diastereoselectivity of >40 : 1.[9] Epoxidation of 8 (9.5 g, 29 mmol) using TBHP (6 ml, 44 mmol, 70% solution) and $VO(acac)_2$ (ca 80 mg) in CH_2Cl_2 (90 ml) (0 °C, 15 h) gave the corresponding epoxide as the sole product which was then protodesilylated[12] using Bu^tOK (3.26 g, 29.1 mmol) and $Bu^n{}_4NF$ (7.61 g, 29.1 mmol) in THF (94 ml) (0 °C, 10 min) to give 9 (6.5 g). Acetylation of 9 followed by oxidation[13] of the resulting acetate 10 with $NaIO_4$ (24.5 g, 115 mmol) and $RuCl_3 \cdot 3H_2O$ (120 mg, 0.46 mmol) in a mixture of CCl_4 (50 ml), CH_3CN (50 ml) and H_2O (100 ml) (room temperature, 1.5 h) furnished the ester 11 (4.72 g, 59% from 8) after esterification and deacetylation. Finally oxidative cleavage of 11 (4.72 g, 17.2 mmol) using $NaIO_4$ (11.05 g, 51.6 mmol) in Pr^iOH (80 ml), AcOH (30 ml) and H_2O (80 ml) (20 °C, 25 h) afforded the aldehyde 1 (2.16 g, 73%, $[\alpha]_D^{25}$ +50.6° (c 0.83, $CHCl_3$)) after purification by chromatography. The ^1H NMR data of 1 prepared here was in accord with the data recorded in the literature.[2,4] Since the reported rotation for 1 have been varied widely (from +24.5° to +74.9°)[2-5] because of the great tendency to hydrate, enantiomeric purity of 1 was confirmed by transformation to the epoxy alcohol 2 ($[\alpha]_D^{25}$ -34.9° (c 0.50, $CHCl_3$);lit. 4, $[\alpha]_D^{24}$ -37.4° (c 0.27, $CHCl_3$), lit. 5a, $[\alpha]_D^{24}$ -33.6° (c 0.36, $CHCl_3$)).

Using the same strategy used above, we prepared 1.43 g of 2(R),3(S)-epoxyoctanal (13) ($[\alpha]_D^{25}$ +79.4° (c 1.00, Et_2O)), intermediate for synthesis of 14(S),15(S)-LTA_4,[14] starting with 2.47 g of (R)-3 (53% overall yield and >40 : 1 overall diastereoselectivity) (Scheme 2). Noteworthy is the fact that the final oxidative cleavage of 12 to 13 under the same conditions used



Scheme 1. i, $MeC(OEt)_3$, EtCOOH (cat); ii, $LiAlH_4$; iii, PBr_3, C_5H_5N; iv, $NaC{\equiv}CH$, Me_2SO; v, MeLi then Me_3SiCl; vi, Bu^iMgBr, $(\eta\text{-}C_5H_5)_2TiCl_2$ (cat), Et_2O then CuI, THF, Me_2S; vii, (R)-3; viii, TBHP, $VO(acac)_2$ (cat); ix, Bu^tOK, $Bu^n{}_4NF$, THF; x, Ac_2O, C_5H_5N; xi, $NaIO_4$, $RuCl_3{\cdot}3H_2O$ then CH_2N_2, xii, NaOMe, MeOH; xiii, $NaIO_4$, AcOH, Pr^iOH, H_2O.



Scheme 2. i, Bu^iMgBr, $(\eta\text{-}C_5H_5)_2TiCl_2$ (cat), Et_2O then CuI, Me_2S, THF; ii, (R)-3; iii, TBHP, $VO(acac)_2$ (cat); iv, Bu^tOK, $Bu^n{}_4NF$, THF; v, H_5IO_6, THF, H_2O.

for 11 was very slow and we executed this transformation using H_5IO_6 in THF and H_2O (10-15 °C, 24 h). Enantiomeric purity of 13 was determined by converting 13 into 2(S),3(S)-epoxy-1-octanol ($[\alpha]_D^{25}$ -44.0° (c 1.01, $CHCl_3$); lit. 14, $[\alpha]_D$ -44° (c 1.0, $CHCl_3$)) using $NaBH_4$ in MeOH.

The large-scale synthesis of the optically active epoxy aldehydes 1 and 13 using the operationally simple reactions are described. This synthesis can be applied to other optically active 2,3-epoxy aldehydes including

(Z)-2(R),3(S)-epoxyundec-5-enal, the intermediate in the synthesis of 11,12-LTA_4.[15]

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