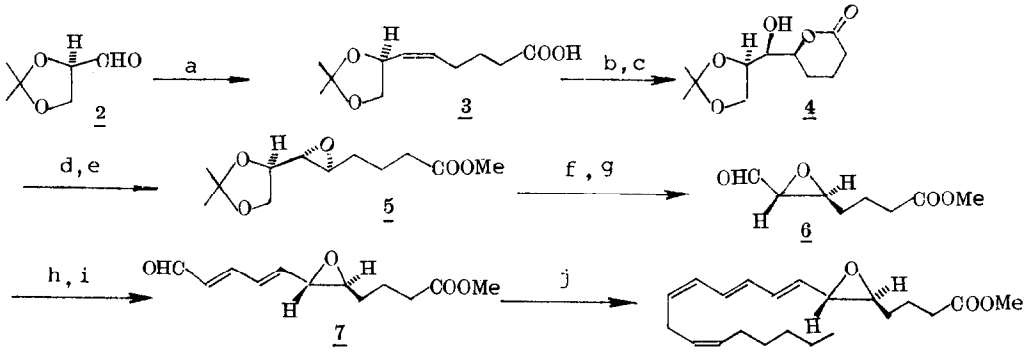
Tetrahedron Letters,Vol.27,No.38,pp 4583-4584,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

A FACILE STEREOSELECTIVE SYNTHESIS OF LEUKOTRIENE A_4(LTA_4) METHYL ESTER

Yanfang Wang, Jincui Li, Yulin Wu* (The First Department)
Yaozeng Huang*, Lilan Shi, Jianhua Yang (The Ninth Department)
Shanghai Institute of Organic Chemistry, Academia Sinica
345 Lingling Lu, Shanghai, China

Abstract: A facile synthesis of LTA_4 1 methyl ester was achieved according to Scheme 1, in which the key intermediates 6 and 7 were prepared with the new procedures conveniently, stereoselectively and in good yields.

The important mediator of anaphylaxis, leukotrienes,[1] especially LTA_4 1, has become the synthetic target of many organic chemists, because 1 is also the biological and chemical precursor of the other leukotrienes C_4, D_4 and E_4.[2] Herein we would like to report a facile stereoselective synthesis of its methyl ester. The strategy of our synthesis involves: the synthesis of 5 through an asymmetric inductive dihydroxylation of 3, followed by lactonization and ring opening; a building up of an E,E-conjugated dienyl aldehyde 7 from an aldehyde 6 by means of an arsonium salt (Scheme 1).



a, $Br^-(C_6H_5)_3\overset{+}{P}CH_2(CH_2)_3COOH$, $CH_3\overset{-}{S}O\overset{+}{C}H_2Na$, CH_3SOCH_3; b, OsO_4-NMO, acetone-H_2O; c, DCCI, DMAP, CH_2Cl_2; d, MsCl, Py, DMAP; e, CH_3ONa, CH_3OH; f, AcOH-H_2O-dioxane; g, $NaIO_4$; h, $OHC-CH=CHCH_2\overset{+}{A}s(C_6H_5)_3Br^-$, K_2CO_3, Et_2O-THF-trace H_2O; i, I_2; j, $I^-(C_6H_5)_3\overset{+}{P}CH_2CH_2CH=CHC_5H_{11}$, BuLi, THF-HMPA.

Starting from the readily available acetonide of D-glyceraldehyde 2 as the chiral template, compound 3 was obtained by Wittig reaction in the usual manner. Rokach et al.[3] have reported that the trans isomer of 3 could be selectively reacted with mCPBA to give the epoxide, but unfortunately in favor(2:1) of the undesired enantiomer of 5. So we considered that cis addition to the cis double bond followed by configuration inversion at C_6 will yield the desired 5S, 6R

product. Thus, compound 3 underwent dihydroxylation selectively with OsO_4-NMO (N-methyl morpholine oxide),[4] and the crude product was directly treated with DCCI(N,N'-Dicyclohexylcarbodiimide), DMAP(4-dimethylaminopyridine) in CH_2Cl_2 to afford 5S,6S-hydroxy-lactone 4 in 75% yield, accompanied with a small amount of the 5R, 6R isomer. The proportion of the two isomers is 9:1. The stereoselectivity of this reaction is much higher than that of epoxidation or iodolactonization.[5] The compound 4[6] could easily be purified by column chromatography. Mesylation of the free hydroxy group followed by treatment with sodium methoxide gave the desired 5S, 6R-epoxide 5[3] in 75% yield. Deprotection of the vic-glycol and C-C bond cleavage with sodium periodate in one pot yielded the known epoxyaldehyde 6[7] in 55% yield. In extension of our method of formylolefination of aldehyde[8], formyl-enyl-olefination of epoxyaldehyde 6 by means of 3-formylallyltriphenylarsonium bromide and potassium carbonate gave trans-trans and cis-trans products, in favor of the former (85:15)[9] in 80-85% yield. Treatment with iodine afforded pure trans,trans-$\alpha,\beta,\gamma,\delta$-aldehyde 7, from which the title compound was synthesized according to the known procedure. The methyl ester of synthetic 1 has m.p. 28.5-30.5°C, $[\alpha]_D^{23}$-26.4, (C 0.39, cyclohexane) and the other spectroscopic data are in complete agreement with that reported in literature.[7a,b]

ACKNOWLEDGEMENT We thank the Science Funds of the Chinese Academy of Sciences for the financial support.

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5. Our experiments show that peracid epoxidation gave both isomers in the proportion of 3:2, while iodolactonization followed by alkali-treatment gave both isomers in the proportion of 5:2.
6. Compound 4: m.p. 99-100°C, $[\alpha]_D^{22}$+13.7 (C 0.98, Chloroform). Spectroscopic data and elemental analysis are in agreement with the given structure.
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(Received in Japan 31 May 1986)