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A NOVEL STEREOSPECIFIC SYNTHESIS OF (±)-LEUKOTRIENE A_4(LTA_4),METHYL ESTER

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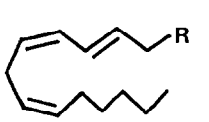
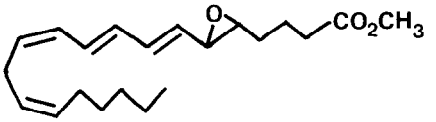
Abstract The reaction of the phosphonate 1 with the epoxyaldehyde 2 is reported as the key step in a novel stereospecific synthesis of (±)-LTA_4, methyl ester 3

The possible implication of the leukotrienes LTC_4, D_4 and E_4 in immediate hypersensitivity reactions such as allergic asthma, has prompted much interest in the synthesis of these mediators [1-4] The key intermediate leukotriene A_4 (LTA_4), methyl ester serves as a common precursor to LTC_4, D_4 and E_4 via its coupling with the appropriate thiol followed by base hydrolysis [4] This paper describes a new synthesis of (±)-LTA_4, methyl ester 3 via the stereospecific coupling of the phosphonate 1 with the epoxyaldehyde 2 [5] Clearly, the synthesis may also be applied to the preparation of optically active 3 by coupling the known[6] optically active form of 2 with 1 under the same conditions



1 R = $P(O)(OEt)_2$
7 R = OCOEt
8 R = OH
9 R = Br
10 R = $P^+Ph_3Br^-$

2



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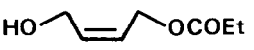

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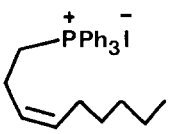

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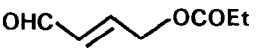

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Treatment of commercially available Z-2-butene-1,4-diol with 0 75 equivalents of propionic anhydride in acetone (reflux, 7h) afforded, after filtration and concentration, the crude monopropionate 4, which was washed consecutively with petrol and brine (to remove dipropionate and unreacted diol) to give pure 4[7] in 55% yield after distillation[8] [b p 90°/2mm] Oxidation of 4 with 1 1 molar equivalents of pyridinium chlorochromate in dichloromethane (23°, 2 5h) proceeded with concomitant double bond isomerisation to give exclusively the E -enal 5 in 54% yield [b p 115°/14mm] On a large scale, 5 was more

conveniently prepared by stirring a solution of 4 in dichloromethane with an aqueous solution containing 0 4 molar equivalents of sodium dichromate and 3 2 equivalents of sodium bisulphate (23°,23h) to give 5 in 48% yield after distillation Wittig coupling of 5 with the ylid derived from the phosphonium salt 6[2] (1 equivalent of n-butyllithium in tetrahydrofuran-hexamethylphosphoramide,-78°, 1h) proceeded stereospecifically to give the Z-coupled product 7 which on treatment with potassium carbonate in methanol (23°, 3h) afforded the alcohol 8 in 72% overall yield from 5 Exposure of 8 to 1 2 equivalents of carbon tetrabromide and 1 3 equivalents of triphenylphosphine in dichloromethane (0°, 1h) afforded the labile bromide 9 which was treated directly with 1 7 equivalents of triethyl phosphite (23°, 3 days then 80°, 3h) to give the phosphonate 1 as a colourless oil in 55% yield from 8 Addition of a 1 1 mixture of 1 and 2[5] to 1 1 equivalents of sodium hydride in tetrahydrofuran containing 0 04 equivalents of 15-crown-5 (0°, 1h) gave (±)-LTA_4, methyl ester 3 in 34% yield after quenching with water, extraction into ether and purification by flash column chromatography using triethylamine deactivated silica The 250 MHz PMR spectrum of this material did not reveal contamination by other isomers of 3, and was identical to a spectrum of 3 prepared by a different route [9] The crude bromide 9 was also treated with an excess of triphenylphosphine in toluene (40°, 16h) to give the phosphonium salt 10 in 68% yield from 8 In contrast to the phosphonate 1, coupling of the ylid derived from 10 with the aldehyde 2 (1 equivalent of n-butyllithium, toluene, -78°, 1h) proceeded non-stereospecifically to give a 54% yield of a 1 1 mixture of 3 and the corresponding 7-Z-isomer of 3[10] as determined by 250 MHz PMR [9] The preparation and subsequent separation of 7-Z-LTD_4 from a mixture of 3 and its 7-Z-isomer has recently been reported [9]

REFERENCES AND NOTES

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3 E J Corey, D A Clark, A Marfat and G Goto, Tetrahedron Letters, 1980, 21, 3143

4 J Rokach, R N Young, M Kakushima, C K Lau, R Seguin, R Frenette and Y Guindon, Tetrahedron Letters, 1981, 22 , 979

5 Prepared in three steps from methyl 4-formylbutyrate, J G Gleason, D B Bryan and C M Kinzig, Tetrahedron Letters, 1980, 21, 1129 We are grateful to Dr J G Gleason for supplying experimental details

6 For example see J Rokach, R Zamboni, C K Lau and Y Guindon, Tetrahedron Letters, 1981, 22, 2759, D P Marriot and J R Bantick, ibid, 1981, 22, 3657, and references cited therein

7 The corresponding monoacetate, from Ac_2O, was very difficult to purify

8 All stable intermediates were characterised by microanalysis, PMR, IR and, where applicable, UV spectroscopy

9 I Ernest, A J Main and R Menassé, Tetrahedron Letters, 1982, 23, 167

10 This ratio was remarkably insensitive to changes in reaction conditions

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