Tetrahedron Letters,Vol.23,No.34,pp 3463-3466,1982 0040-4039/82/343463-04$03.00/0
Printed in Great Britain

TOTAL SYNTHESIS OF 5-DESOXYLEUKOTRIENE D. A NEW AND USEFUL EQUIVALENT OF THE 4-FORMYL-TRANS,TRANS-1,3-BUTADIENYL ANION

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Summary: The first total synthesis of 5-desoxyleukotriene D (14) is reported. The route of synthesis utilizes a novel method for five-carbon chain extension. The availability of 14 allowed experimental demonstration that the 5-hydroxyl function is important for biological activity of the slow reacting substances.

The slow reacting substances, leukotrienes C, D, and E, are of considerable interest as a new family of highly active biological regulators which also can serve as mediators of pathological states such as asthma.[1] One of the most significant chemical problems concerning the action of leukotrienes (LTs) is the question of the molecular binding which triggers biological response. This can be approached by the study of the bioactivity of structural analogs of the leukotrienes, an avenue of investigation which already has yielded significant results.[2,3] Because of the relatively slow onset (several minutes) and prolonged duration (30 min to 2 hr) of action of leukotrienes on the airway, the possibility of covalent bonding to the sites of recognition seems not unreasonable. One such mode of binding might be through δ-lactonization of the leukotriene followed by acylation of a nucleophilic group on the receptor by the eicosanoid C-1 carboxyl (Scheme 1). If this were the case, it follows that the C-5 hydroxyl function would be indispensable to activity. To test this hypothesis it seemed desirable to synthesize the 5-desoxy-leukotrienes for biological studies. The first successful synthesis of a 5-desoxyleukotriene, 5-desoxy LTD (14) is reported herein.

The overall plan of synthesis involved the assemblage of the 20-carbon skeleton by joining methyl 5-formylpentanoate (1) with a synthetic equivalent of the 4-formyl-trans,trans-1,3-butadienyl anion (2) and subsequent coupling with the Wittig reagent 3. Attachment of the S-peptide by nucleophilic displacement at C-6 would complete the synthesis. The conjugate base of trans-1-phenylsulfinylmethyl-1,3-butadiene (5) was selected as a possible equivalent of 2. The synthesis of 5 was accomplished expeditiously by the sequence: (1) reaction of 1-bromo-trans-2,4-pentadiene[4] with 1.28 equiv of thiophenol and 1.6 equiv of anhydrous potassium carbonate in dry acetone at 25°C for 30 min under argon to form the phenylthioether 4, bp 85-90°C at 0.2 mm Hg, in ca. 90% yield and (2) oxidation of 4 with 1.15 equiv of sodium metaperiodate in methanol-water (1.6:1) at 25°C for 20 hr to give 5 in 87% yield after chromatographic purification on a silica gel column as a colorless oil (at 25°C) which solidifies upon storage at -20°C.[5]

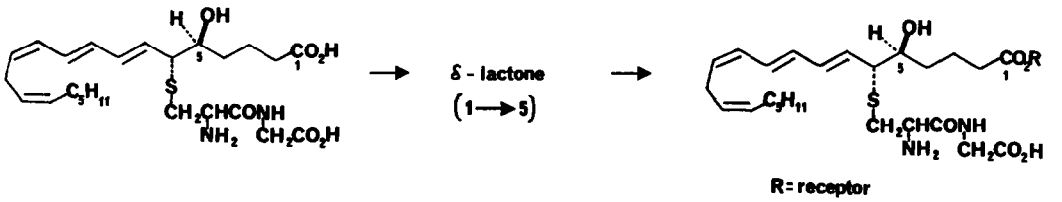
Reaction of 5 in tetrahydrofuran (THF) solution under argon at -78°C with 1 equiv of n-butyllithium for 20 min generated the lithio derivative which was allowed to react with methyl 5-formylpentanoate (prepared by ozonolysis of 1-methoxy cyclohexene) at -78°C for 15 min and then at -40°C for 15 min. The solution of the resulting β-alkoxysulfoxide was treated at -40°C with 1.15 equiv of benzoyl chloride in THF and kept at -40°C to 0°C for 2 hr to complete benzoylation to 6 and at 25°C for 3 hr to allow double [3,2]

sigmatropic rearrangement of 6 to 7. Extractive isolation and chromatography on silica gel afforded a mixture of two sulfoxide esters 7 in 60% overall yield from 5. The unusual facility of the double [3,2] sigmatropic rearrangement of 6 to 7 is noteworthy as is the fact that the driving force for internalization of the diene unit provides sufficient stabilization to produce a ratio for 7/6 in excess of 20.

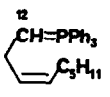
Pummerer rearrangement of 7 to the acetoxy sulfide 8 was effected by reaction of 7 (2.9 mmole) in acetic anhydride (3.5 ml) and 2,6-lutidine (12 mmole) at 0°C with a mixture of trifluoroacetic anhydride (10 mmole) and anhydrous sodium acetate (10 mmole) in acetic anhydride (5 ml).[7] After 80 min at 0°C and 20 min at 25°C crude 8 was isolated by concentration in vacuo and extractive separation. Hydrolysis of 8 in 4:1 acetonitrile-water by successive addition of excess calcium carbonate and mercuric chloride (1.7 equiv) at 0°C for 2.5 hr furnished after extractive isolation (including washing of the organic layer with saturated NH_4Cl to remove mercury compounds) and chromatography on silica gel the dienal 9. UV max 270 nm (ϵ 29,000), (65% overall yield from 7) which because of its instability was used immediately in the next step.

Addition of the dienal 9 to the ylide 3 (1.2 equiv) in THF containing 20 equiv of hexamethylphosphorictriamide at -78°C and reaction at -78°C for 10 min, -65° to -60°C for 70 min and -60° to -20°C for 60 min afforded after quenching with wet ether containing triethylamine, extractive isolation, and rapid chromatography on silica gel with 85:15:1 hexane-ether-triethylamine the tetraene 10, UV max (CH_3OH) 273.5 nm (sh at 265, 285 nm), ϵ 51,000, as a colorless oil (84% yield). Triethylamine was used during chromatography of 10 and 11 because of their susceptibility to acid-catalyzed decomposition. A ratio of 11-cis/trans of ca. 20 was determined by HPLC analysis of tlc chromatographed 10 using a Waters Associates μ-Porasil column with a mobile phase of 80:20:0.1 hexane-methylene chloride-2-propanol.

Cleavage of the benzoyl protecting group of 10 was effected by reaction with 5 equiv of anhydrous potassium carbonate in methanol at 25°C until tlc analysis indicated the process was essentially complete (ca. 10 hr reaction time) to give the hydroxy ester 11 in 95% yield after chromatography on silica gel (1:1:0.01 ether-hexane-triethylamine). The triene alcohol 11 was converted to the highly reactive mesylate 12 by successive treatment in methylene chloride at -50°C with 1.8 equiv of triethylamine and 1.5 equiv of methanesulfonylchloride for 20 min and this was coupled in situ with a solution of the potassium thiolate of N-trifluoroacetyl-L-cysteinylglycine methyl ester[9] prepared just before use from reaction of the dipeptide ester in THF solution at -30°C with a THF solution of potassium t-butoxide. The coupling was carried out using 4 equiv of potassium thiolate (final conc. 0.36 M) and 10 equiv of hexamethylphosphorictriamide in ca. 2:1 THF-CH_2Cl_2 at -40°C for 20 min, -15°C for 1 hr, -10°C for 2.5 hr, and 0°C for 5 hr. The reaction mixture was treated with pH 7 buffer and the crude coupling product was isolated by extraction and chromatography on silica gel tlc plates (using ether containing a little triethylamine for development; R_f 0.5 - 0.6). The coupling product so obtained (total yield 31%) could be separated into six components by HPLC using a 5μ aminopropyl bonded Spherisorb column derivatized with N-3,5-dinitrobenzoyl-D-phenylglycine (Pirkle 1-A column, Regis Co., Morton Grove, IL)[10] using 1:20:80 2-propanol-methylene chloride-hexane. The first and fourth peaks (retention vols. 7.5 and 10.2, respectively) which were identified as the desired protected 5-desoxy-LTD diastereomers 13 exhibited UV max (CH_3OH) at



SCHEME 1



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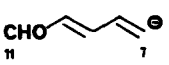

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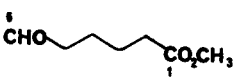
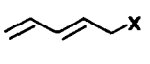
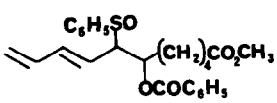


1



4, X = SC_6H_5
5, X = SOC_6H_5



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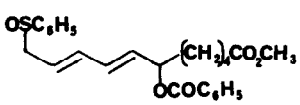
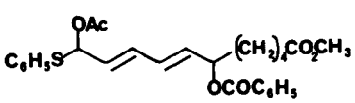


7



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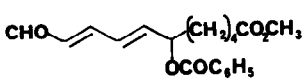

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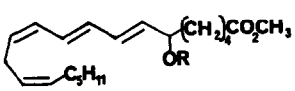
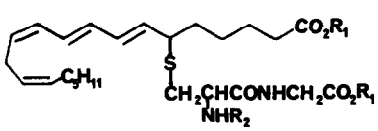


10, R = COC_6H_5
11, R = H
12, R = SO_2CH_3



13, $R_1 = CH_3$, $R_2 = CF_3CO$
14, $R_1 = R_2 = H$

280 nm with shoulders at 270 and 290 nm, and pmr spectra indicative of the 7,9-trans,11-cis geometry of the triene unit (pmr with spin decoupling at 270 MHz[11]). Demethylation of each isomer of 13 using 50 equiv of 0.1 M lithium hydroxide-methanol (1:1) under argon at 0° for 1.5 hr (monitored by HPLC using a C_{18} column with 74:26:0.074 CH_3OH-H_2O-HOAc buffered to pH 5.6 with NH_4OH) gave each of the two diastereomeric N-trifluoroacetyl derivatives of 14, UV max (CH_3OH) at 280 nm (sh at 270, 290 nm), R_v 10 (from diastereomer 13 corresponding to peak 1 from the Pirkle column) and R_v 8.5 from 13 corresponding to Pirkle column peak 4). Each diastereomer was rapidly converted by soybean lipoxygenase to a conjugated tetraene, UV max 309 nm, a diagnostic test for 11,14-cis ethylenic units.[12] N-Deprotection of the N-trifluoroacetyl derivatives of 14 of R_v 10 and R_v 8.5 (150 equiv of 0.35 M LiOH in 1:1 CH_3OH-H_2O at 25°C for 8 hr) afforded two pure diastereomers 14 each R_v 7.0 (HPLC column as above), UV max (CH_3OH) at 280 nm (sh at 270, 290 nm).

Each of the synthetic diastereomers of 5-desoxy-LTD (14) was found to have < 1% of the activity of LTD in the usual assays for activity of slow reacting substances with guinea pig ileum and pulmonary parenchymal strips,[13] showing that the 5-hydroxyl function is important for the bioactivity of the slow reacting substances. This research also establishes the value of the 1,5-sulfinyl rearrangement strategy and the use of the reagent 5 as an equivalent of anion 2 in synthesis.[14]

References and Notes

1. See, for example, J. W. Weiss, J. M. Drazen, N. Coles, E. R. McFadden, Jr., P. F. Weller, E. J. Corey, R. A. Lewis and K. F. Austen, Science, 216, 196 (1982).
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4. K. Mori, Tetrahedron, 30, 3807 (1974).
5. Satisfactory infrared, nuclear magnetic resonance, and mass spectroscopy data were obtained for each isolated synthetic intermediate.
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13. We are grateful to Drs. Robert A. Lewis and Jeffrey M. Drazen of the Harvard Medical School for these results which will be presented in full detail elsewhere.

14. This research was assisted financially by the National Institutes of Health and the National Science Found.

(Received in USA 11 June 1982)