Tetrahedron Letters,Vol.30,No.26,pp 3377-3380,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Maxwell Pergamon Macmillan plc

CONFORMATIONALLY RESTRICTED LEUKOTRIENE ANTAGONISTS. ASYMMETRIC SYNTHESIS OF SOME NOR-LEUKOTRIENE D_4 ANALOGS

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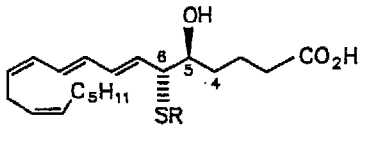
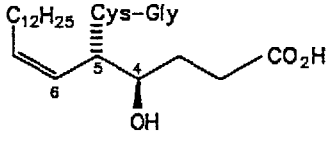
Summary: The enantiomeric pair of conformationally-restricted nor-LTD_4 analogs 10 and 11 have been synthesized stereoselectively from (S)-2-cyclohexen-1-ol.

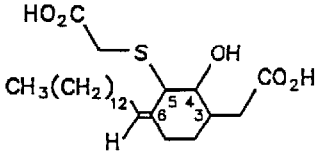
Due to our continuing interest in the stereoselective syntheses of conformationally-restricted LTD_4 analogs[1], we were attracted by recent reports[2] that 2-nor-leukotriene analogs such as SKF 101132 possess significant LTD_4 antagonist activity. The correlation observed



LTD_4 SR=Cysteinylglycinyl



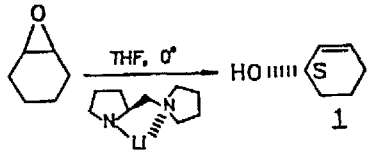
SKF 101132



10 (3R,4S,5R)
11 (3S,4R,5S)

between absolute configuration and antagonist/agonist potency for these compounds prompted us to synthesize the nor-analogs 10 and 11.

From a practical point of view, a stereocontrolled synthesis starting with chiral material would offer the advantage of final products having defined relative stereochemistry and absolute configuration. The syntheses of 10 and 11 from (S)-2-cyclohexen-1-ol 1 is outlined in Scheme I. The hydroxyl group of 1 is used as a handle to introduce all the requisite functionalities. This approach, whereby both enantiomers 10 and 11 could be derived from a common chiral starting material 1, appeared to be synthetically expedient.



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Rearrangement of meso-cyclohexene oxide with the chiral lithium base prepared from (S)-(+)-2-(1-pyrrolidine)methylpyrrolidine[3] furnished (S)-2-cyclohexen-1-ol 1 ($[\alpha]_D^{20}$-97°(c 1.35, $CHCl_3$)) in 60% yield and 67% enantiomeric excess (ee)[4]. Protection of 1 as the t-butyldiphenylsilyl ether,[5] followed by peracid epoxidation afforded an intermediate trans-epoxyether[6] which was rearranged[7] to the mono-protected diol 2 in 70% overall yield. The acetic acid side chain was introduced with complete control of stereochemistry at this stage by an orthoester Claisen rearrangement[8] of 2 which gave the ester 4 in 84% yield.

The key intermediate 6 ($[\alpha]_D^{20}$ + 30° (c 1.99, $CHCl_3$)) was prepared in 48% yield by a three-step sequence involving deprotection with fluoride, hydroxyl-assisted epoxidation[9] and Swern oxidation[10]. The completion of the synthesis of 10 utilized our previously published procedure.[1] Thus, stereoselective Wittig olefination of 6[11] followed by regiospecific epoxide opening of the resulting Z-olefin 8[12] ($[\alpha]_D^{20}$ - 39° (c 1.65, $CHCl_3$) with ethyl 2-mercaptoacetate provided an intermediate di-ester[13] ($[\alpha]_D^{20}$ + 39° (c 1.96, $CHCl_3$)) which was subsequently saponified to di-acid 10[14] ($[\alpha]_D^{20}$ + 52°(c 1.00, $CHCl_3$)) in 21% overall yield.

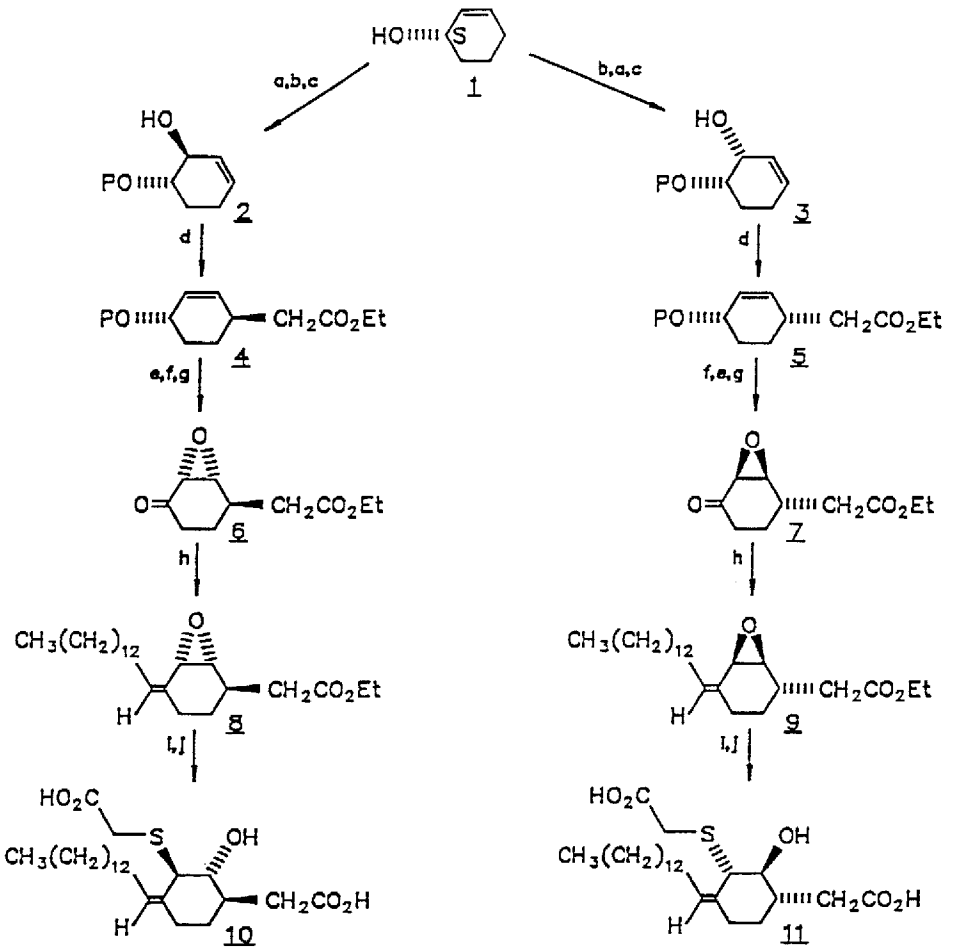
For the synthesis of enantiomer 11, alcohol 1 can be efficiently converted directly to cis-monoprotected diol 3 in three steps in 65% overall yield (Scheme I). Orthoester Claisen rearrangement as above then gave 5 in 83% yield. Epoxidation of the t-butyldiphenylsilyl protected alcohol 5 from the less hindered face followed by a two-step conversion to epoxy-ketoester 7 ($[\alpha]_D^{20}$ - 36° (c 1.71, $CHCl_3$)) was achieved in 45% yield.

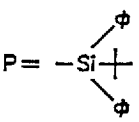
The synthesis of 11 from 7 was essentially the same as that described above for the conversion of 6 to 10. Wittig reaction yielded the Z-olefin 9[12] ($[\alpha]_D^{20}$ + 33° (c 1.04, $CHCl_3$)). Treatment with ethyl 2-mercaptoacetate opened the epoxide of 9 in a regiospecific manner and the intermediate di-ester[13] ($[\alpha]_D^{20}$ - 44° (c 1.02, $CHCl_3$)) was saponified with ethanolic KOH to afford the enantiomeric di-acid 11[12] ($[\alpha]_D^{20}$ - 60° (c 1.12, $CHCl_3$)) in about 20% overall yield from 7.

In summary, chiral alcohol 1 can be prepared in a practical manner in 67% ee. Utilization of this alcohol as a starting material led to the stereocontrolled syntheses of the enantiomeric di-acids 10 and 11. These conformationally-restricted nor-LTD_4 analogs were found to be effective as LTD_4 antagonists.[15]

Acknowledgements: We thank Dr. M. Whalon (MDRI-Indianapolis) and R.J. Barbuch (MDRI-Cincinnati) for their assistance in obtaining analytical data.

SCHEME I



P=  (TBDPS)

CONDITIONS: a) TBDPS-Cl, imidazole, DMF; b) MCPBA, CH_2Cl_2, 0°C;
c) $LiNEt_2$, ether, reflux(20h); d) $CH_3C(OEt)_3$ o-xylene,
$CH_3CH_2CO_2H$(cat.), reflux(20h); e) $(n\text{-}Bu)_4\overset{\oplus\ominus}{N}F$, THF, rt(2h);
f) MCPBA, CH_2Cl_2, 0°C(16h); g) $(COCl)_2$, DMSO, $N(Et)_3$,
CH_2Cl_2, $-70° \longrightarrow$ rt; h) $CH_3(CH_2)_{13}\overset{\oplus}{P}\emptyset_3\overset{\ominus}{Br}$, nBuLi, THF,
$-40° \longrightarrow$ rt; i) $HSCH_2CO_2Et$, EtOH, Et_3N, rt(18h);
j) KOH, EtOH, H_2O, rt(6h).

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12) The Z/E ratio of 5-6/1 was determined on the crude product by using 60-MHz ^1H NMR.

13) The 300-MHz ^1H NMR of this intermediate di-ester displayed a signal for the olefinic proton of δ5.46 (1H, t) which distinguishes it from an Sn2' product. Under these conditions, only the Sn2 product could be detected.

14) These compounds gave satisfactory spectra (IR, NMR, MS) and elemental analyses.

15) Dr. T.H. Gieske (MDRI-Cincinnati), unpublished results.

(Received in USA 11 April 1989)