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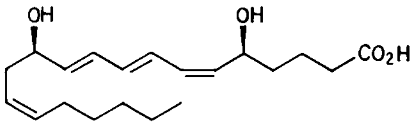
STEREOSELECTIVE SYNTHESIS OF Z-DISUBSTITUTED OLEFINS VIA 2,3-SIGMATROPIC REARRANGEMENTS. AN APPROACH TO LEUKOTRIENES.

Aston D. Kaye and Gerald Pattenden*
Department of Chemistry, The University, Nottingham, NG7 2RD.
Stanley M. Roberts
Glaxo Research Ltd., Greenford, Middlesex, UB6 OHE.

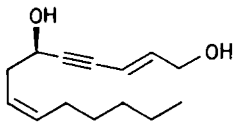
Summary: Stereoselective 2,3-sigmatropic rearrangement of the propargyl 2-silylallyl ether(5) leads to the vinyl silane (7), which, after protiodesilylation and palladium catalysed coupling to 3-bromoprop-2-enol, produces the Z,E-dienynol(10) a key intermediate in leukotriene synthesis.

Sigmatropic rearrangements of all types have been used in a number of ways to control stereochemical detail in a wide range of synthetic procedures.[1] In connection with synthetic investigations amongst the leukotriene family of arachidonic acid metabolites, e.g. leukotriene B_4(1)[2] we required a flexible synthetic entry to Z,E-dienes of the type shown in (2). In this Letter we outline a solution to this interesting problem, which is based on a novel stereoselective 2,3-sigmatropic rearrangement of an appropriate propargyl 2-silylallyl ether (viz 5→7) followed by protodesilylation to the Z-enynol silyl ether(6) and coupling of the latter to E-3-bromoprop-2-enol in the presence of a palladium catalyst.



(1)

$\Rightarrow$



(2)

A Grignard reaction between hexanal and trimethylsilylvinyl magnesium bromide first led to the secondary alcohol(3; 60%), which under phase-transfer catalysed conditions($Bu_4\overset{+}{N}.H\overset{-}{S}O_4$, 50% aq. NaOH) with propargyl bromide gave rise to the propargyl 2-trimethylsilylallyl ether(4; 71%). Treatment of (4) with n-butyllithium followed by trimethylsilyl chloride then provided the bis-silane(5). The bis-silane(5) underwent an efficient, stereoselective 2,3-sigmatropic rearrangement at -30°C in tetrahydrofuran in the presence of *n*-butyllithium to produce the *E*-vinylsilane(7) containing less than 20% of the corresponding *Z*-isomer in a combined yield of 84%.[3,4] Treatment of (7) with sodium hydride in dimethylformamide resulted in selective desilylation leading to the vinylsilane(8*a*; 88%). Finally, after protection of (8*a*) as the corresponding *t*-butyldiphenylsilyl ether(8*b*), protiodetrimethylsilylation in the presence of hydriodic acid led to the *Z*-enynol ether(9).[5] A coupling reaction between (9) and *E*-3-bromoprop-2-en-1-ol in the presence of $Pd(PPh_3)_4$-CuI-Et_2NH then gave rise to the key intermediate(2) as its *t*-butyldiphenylsilyl ether(10).[6]

The use of the trimethylsilyl group in (5) to both introduce and control the *Z*-geometry of the double bond in the 2,3-sigmatropic rearrangement-protiodesilylation sequence leading to (9) is quite remarkable, and to our knowledge without precedent. From studies of the stereoselectivity of 2,3-sigmatropic rearrangements by Still and Mitra[7], and others[8], it is clear that the bulky vinyltrimethylsilyl group ensures a transition state for the rearrangement of (5) whereby the pentyl group is pseudo-axial (see formula 6), thereby leading to the *E*-enynol(7). In addition, the propargyl ether grouping itself would also appear to be important in controlling the stereospecificity of the rearrangement of (5), since the corresponding *bis*-allylic ether(11*a*) led to only 33% of the *E*-dienol(12). In related model work, 2,3-sigmatropic rearrangement from the propargyl allyl ethers(11*b*) and (13) devoid of silicon substitution on their allylic residues, produced almost entirely the *E*-carbinols (14) and (15) respectively.

The new stereoselective synthesis of *Z*-disubstituted olefins, taken in conjunction with the known propensity for optically active *bis*-allylic ethers to transfer chirality during 2,3-sigmatropic rearrangement[9] makes the approach to (10) and analogous compounds, described here, a particularly attractive one for development in the leukotriene field. This development, along with others, is now being pursued.

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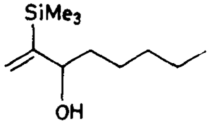

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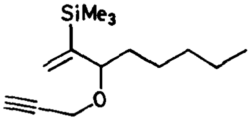

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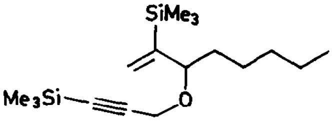

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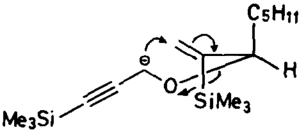

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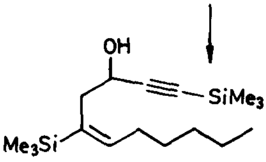

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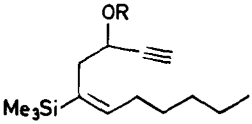
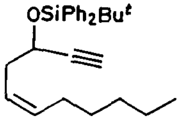


(8)

a, R = H; *b*, R = SiPh$_2$Bu^t



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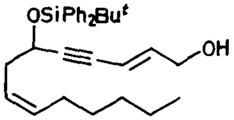

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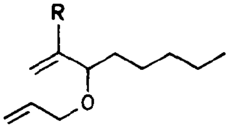
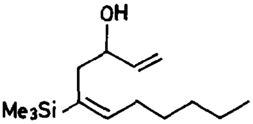


(11)

a, R = SiMe$_3$; *b*, R = H



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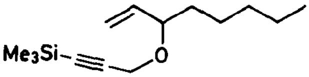

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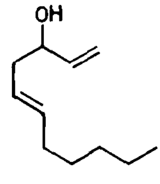

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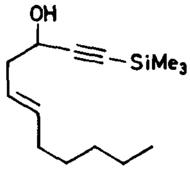

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3. All new compounds showed satisfactory spectral data, in addition to microanalytical and/or mass spectroscopic data.
4. *Z*-*E*-Isomer ratios were determined by a combination of capillary g.c. analysis and inspection of c.m.r. data. The *E*-vinylsilane(7) showed: δ_H0.09(SiMe$_3$), 0.16(SiMe$_3$), 0.88(t, *J*7, $CH_2C\underline{H}_3$), 1.3(m, 6H), 1.92(OH), 2.17(m, 2H), 2.59(m, 2H), 4.35(t, *J*7, $C\underline{H}CH_2$), 5.96(t, *J*7, :C$\underline{H}$); δ_C-0.7(SiMe$_3$), -0.05(SiMe$_3$), 14.1(Me), 22.7(CH$_2$), 29.3(CH$_2$), 31.73(CH$_2$), 32.45(CH$_2$), 38.14(CH$_2$), 62.5(CH), 89.2, 107.0, 135.5, 145.46(:CH)p.p.m. Simple chromatography of the mixture of *Z*-and *E*-isomers of (8), obtained by treatment of (7) with NaH-DMF, was all that was necessary to separate the pure *E*-isomer(8).
5. The silyl ether(9) showed: δ_H2.13(d, *J*2, ≡CH), 4.25(dt, *J*2 and 7, $CH_2C\underline{H}$(O)C≡CH), 5.37(m, 2H); δ_C14.2(Me), 19.4(SiMe$_3$), 22.7(CH$_2$), 27.1(CMe$_3$), 27.5(CH$_2$), 29.4(CH$_2$), 31.6(CH$_2$), 36.4(CH$_2$), 63.8(CH), 72.8, 84.9(≡CH), 123.9(:CH), 133.0(:CH)p.p.m. The *Z*- and *E*-geometries assigned to isomers in this study were made after specific decoupling and nOe experiments.
6. The dienyne(10) showed: δ_H0.88(t, *J*7, $CH_2C\underline{H}_3$),1.08(CMe$_3$), 1.25(m, 6H), 1.76(OH), 1.93(m, CH$_2$), 2.44(m, CH$_2$), 4.15(dd, *J*5.3 and 1.6, $C\underline{H}_2$OH), 4.44(m, C$\underline{H}$-OSiR$_3$), 5.45(m, HC:CH-*Z*), 5.62(dd, *J*15.9 and 1, ≡C.C$\underline{H}$), 6.02(dt, *J*15.8 and 5.2, :$C\underline{H}CH_2$OH), 7.4(m, 6H), 7.73(m, 4H).
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