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# STEREOCONTROLLED (E, Z AND ERYTHRO, THREO) SYNTHESIS OF β-HYDROXYALLYLIC SULPHIDES

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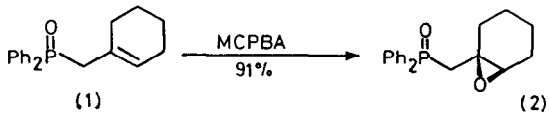
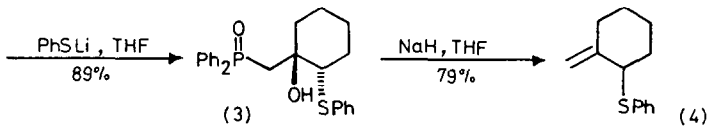
All four isomers of substituted 3-alkylthio-4-hydroxybutenes have been synthesised: both the geometry of the double bond and the relative stereochemistry of the two chiral centres are controlled.

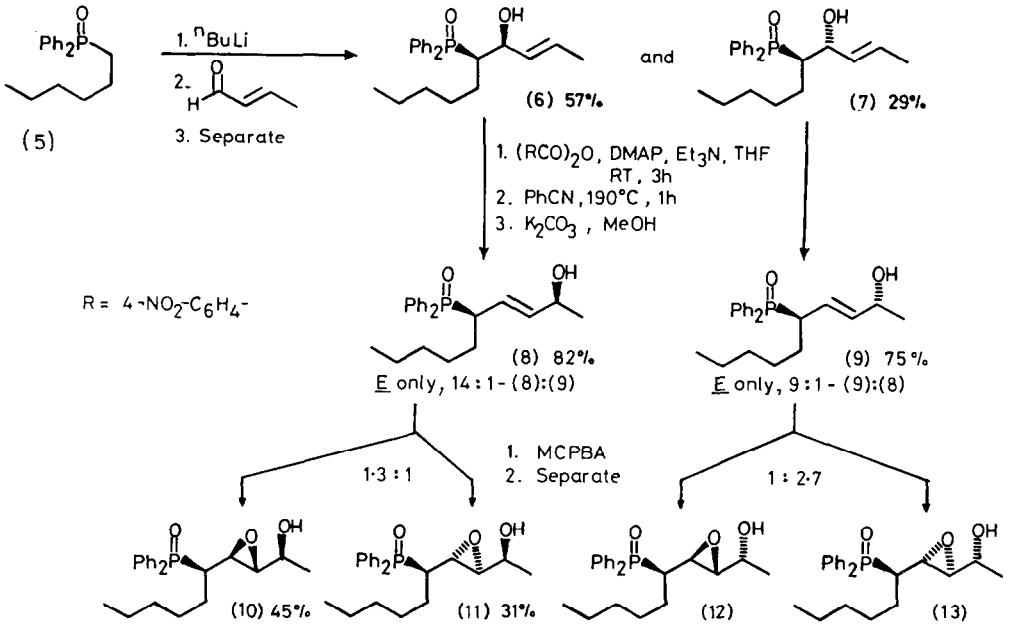
We have recently reported[1] the synthesis of the unstable allylic sulphide (4) via a three stage allylic transposition of the stable allylic phosphine oxide (1). We now report the application of similar reactions to the synthesis of the leukotriene $D_4$ models (17), (18), (26), and (28) with stereochemical control over the two chiral centres and the geometry of the double bond.



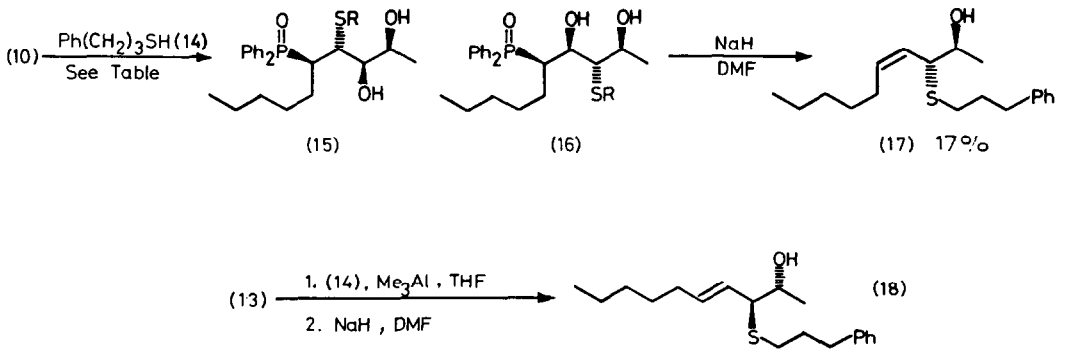




All four isomers of the epoxides (10-13) were available by stereospecific [1,3] hydroxyl transposition[2] of the alcohols (6) and (7) into the alcohols (8) and (9) followed by stereoselective epoxidation[3] (Scheme 1). Attack of thiols on these epoxides at the less hindered site away from the $Ph_2PO$ group would give intermediates (e.g. 16) analogous to (3), but thiols often attack these epoxides with the unwanted regioselectivity.[4] Thus epoxide (10) gave mostly (15) with $Ph(CH_2)_3SH$ (14) under a variety of conditions. Only with $Me_3Al$ was isomer (16) the major product (table). Elimination[5] gave the cis erythro product (17). Similarly, epoxide (13) gave the trans erythro product (18), but only in 6% yield for the two steps.

**Scheme 1**

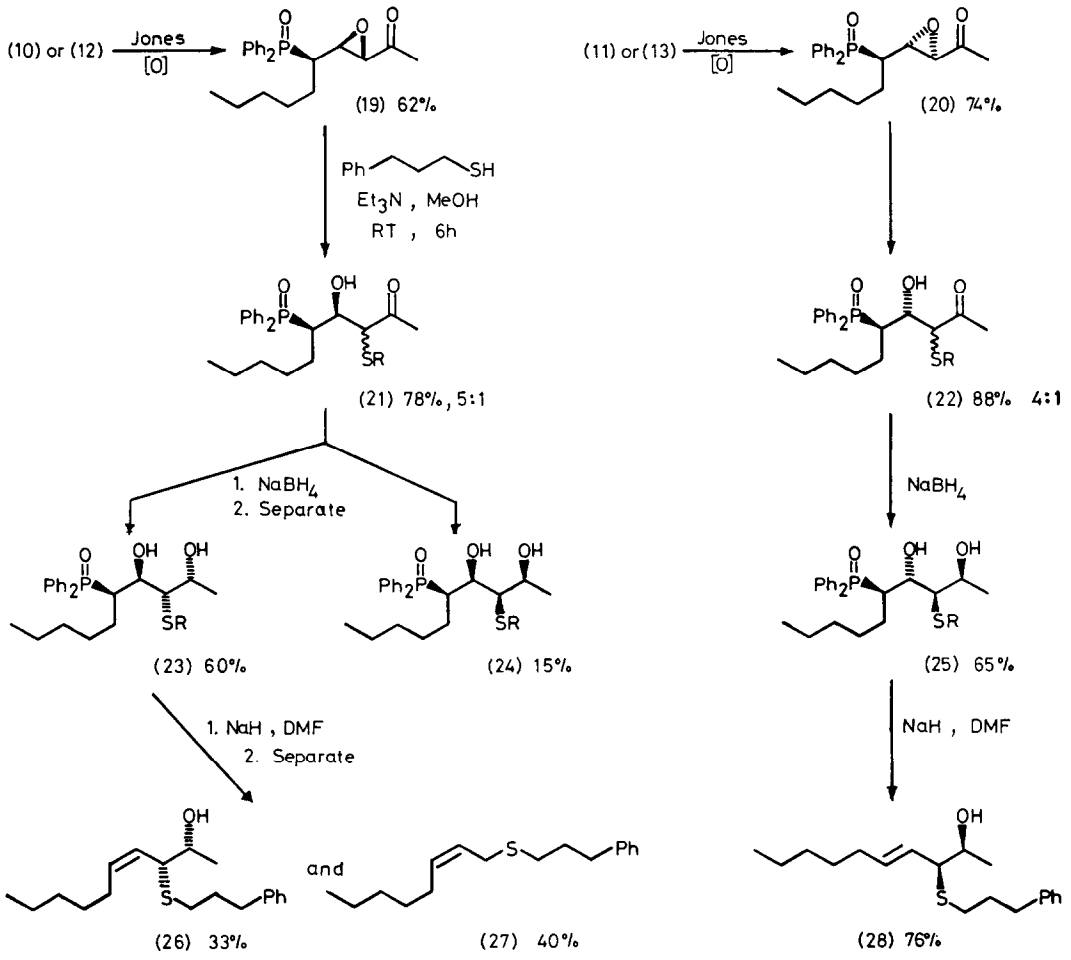


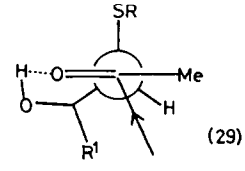

Regiospecific epoxide opening and efficient $Ph_2PO_2^-$ elimination were achieved by prior oxidation to epoxyketones (19) and (20) (Scheme 2). The adducts (21) and (22) were formed with some loss of stereochemical integrity, probably by enolisation of the α-RS ketone after formation, but reduction was totally stereoselective[6] in both cases giving pure Felkin[7] product (25) and the two Felkin[7] products (23) and (24). The normal Felkin selectivity may be enhanced by hydrogen bonding (29).



Stereospecific *syn* elimination[5] of $Ph_2PO_2^-$ from (25) gave pure *E*-threo product (28) in good yield but elimination to give *Z*-threo (26) required more forcing conditions and cleavage to the *Z*-allyl sulphide (27) also occurred.

**Scheme 2**



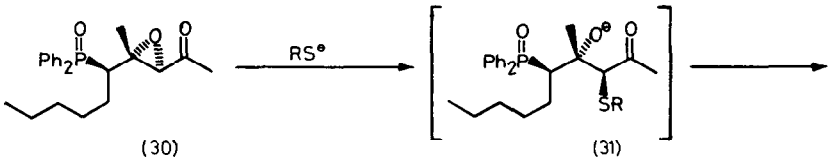



(29)

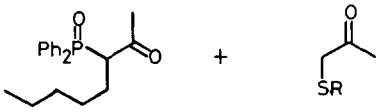
**Table: Addition of Thiol (14) to Epoxide (10)**

| Reaction Conditions | (15):(16) | Yield (15) | Yield (16) |
|---|---|---|---|
| n-BuLi, THF | 5:1 | 60% | - |
| NaH, THF | >6:1 | 66% | - |
| n-BuLi, $AlMe_3$, THF | >6:1 | 71% | - |
| $Me_3Al$, THF | 1:3 | 10% | 31% |
| $HClO_4$, MeCN | - | 12% | - |

Thiol addition to epoxyketone[3] (30) [(14), $Et_3N$, MeOH or (14), LiOMe, MeOH] gave only cleavage products (32) and (35) as the retro-aldol reaction on intermediate (31) is accelerated by the extra methyl group.




(30) (31)




(32) (33)

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References

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4. This is surprising in view of the high steric demand in thiol attack on similar compounds (C.H. Behrens and K.B. Sharpless, Aldrichimica Acta, 1983, **16**, 67) and the large size of the $Ph_2PO$ group.
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