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PHENYLTHIO(PhS) MIGRATION IN THE STEREOCONTROLLED SYNTHESIS OF ALLYLIC ALCOHOLS WITH 1,4 RELATED CHIRAL CENTRES.

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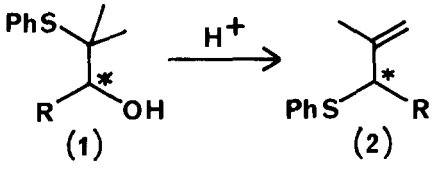
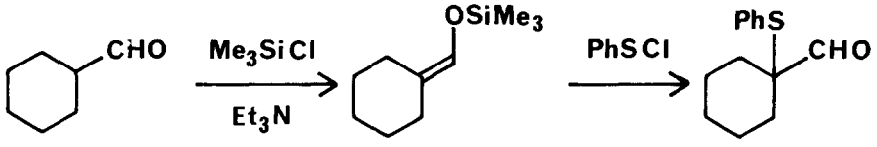
Stereoselective aldol products are transformed by PhS migration into lactones, tetrahydrofurans, and, by subsequent Evans-Mislow rearrangement, into the title compounds with complete stereochemical control.

Our synthesis of allyl sulphides (2) from alcohols (1) by PhS migration[1] should occur stereospecifically with inversion at C* if sulphur participation is involved. If R (in 1) contains other chiral centres, a single diastereoisomer of (1) should give a single diastereoisomer of (2). A neighbouring chiral centre to C* can be set up with nearly complete stereochemical control by a stereoselective aldol reaction.[2] We report that the [1,2]-PhS shift is indeed stereospecific and that aldol products may be thus converted into allylic alcohols with a 1,4 relationship between chiral centres across an E double bond after a [2,3] (Evans-Mislow)[3] rearrangement. Heathcock[4] has similarly relayed aldol stereochemical information by Claisen rearrangements to give 1,4 and 1,5 related chiral centres.



(1) (2)

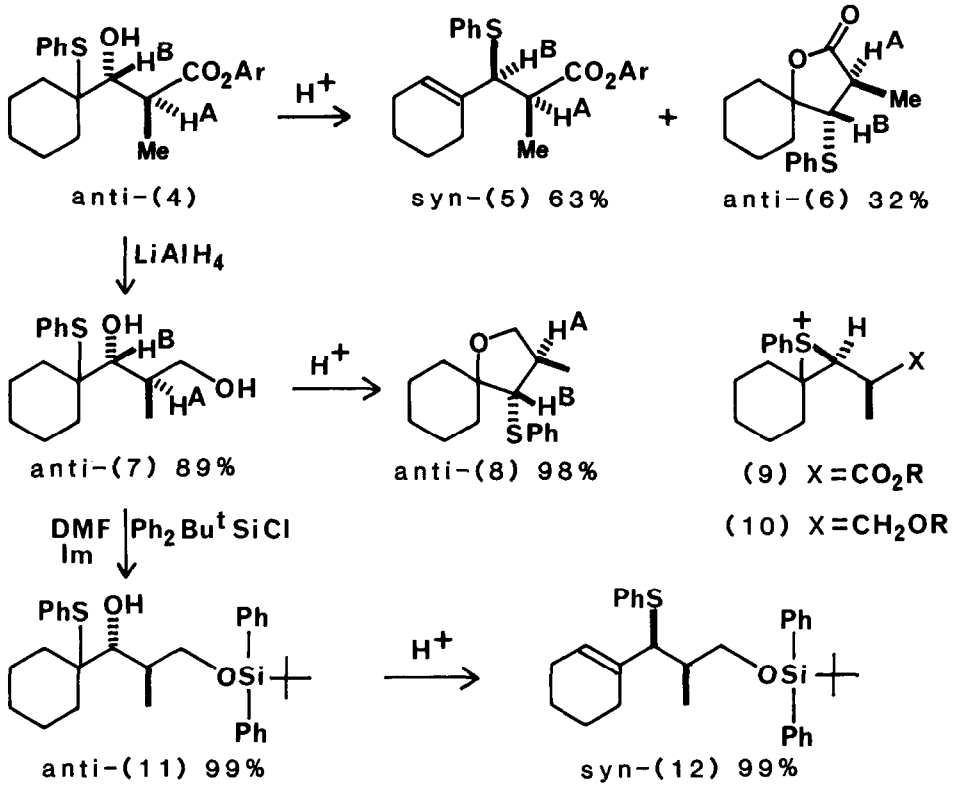


(3)

Addition of the lithium enolate of 2,6-dimethylphenyl propionate[5] to the α-PhS aldehyde (3) gave anti aldol (4) almost exclusively (95:5), pure crystalline anti-(4) being isolated[6] in 84% yield (scheme 1). Rearrangement of ester (4) gave mostly allylic sulphide (5) with some lactone (6). These are both products of a [1,2]-PhS migration, and both rearrangements are

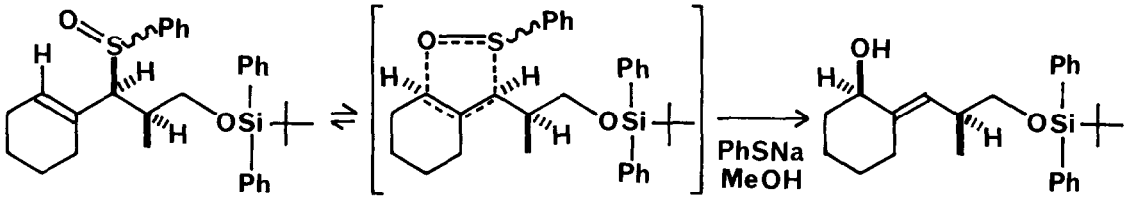
stereospecific.[8] Coupling constants in lactones (6) (J_{AB}) gave the most reliable stereochemical assignment[9] (table) showing that inversion had indeed occurred at C* in the lactone and in the allylic sulphide (5) since both are formed *via* the same episulphonium ion (9).

Scheme 1 (Ar = 2,6-dimethylphenyl)



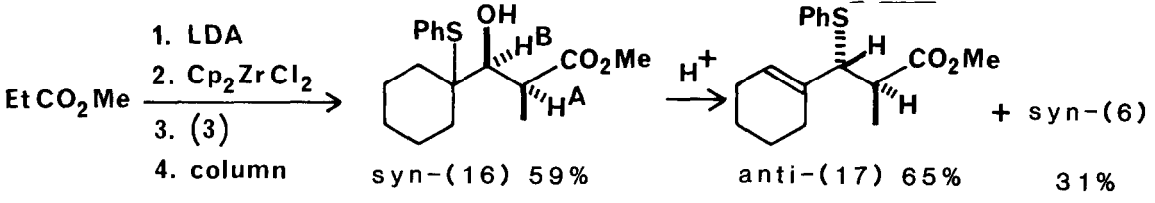
Reduction gave the diol (7) which rearranged in acid by a [1,2]-PhS shift *via* episulphonium ion (10) to give the cyclic ether (8). This was again a single diastereoisomer,[8] almost certainly inverted at C*, though assignments from $J_{3,4}$ are less certain in tetrahydrofurans.[10] Participation by ester or alcohol was prevented by selective silylation of the primary alcohol to give (11) which rearranged stereospecifically[8] to allylic sulphide (12). We assign inverted stereochemistry to (12) by NMR correlation with (5).

Oxidation of the allylic sulphide (12) gave a roughly 1:1 mixture of sulphoxides (13). Evans-Mislow[3] rearrangement of the mixture in MeOH with the thiophile PhSNa gave a single isomer[11] of the allylic alcohol (15). The [2,3] sigmatropic shift is suprafacial, as expected, and prefers the conformation (14) which leads to the *E* double bond.[12] The configuration at sulphur does not affect the stereochemistry of the rearrangement as it merely places the phenyl group in a different conformation in the transition state (14).

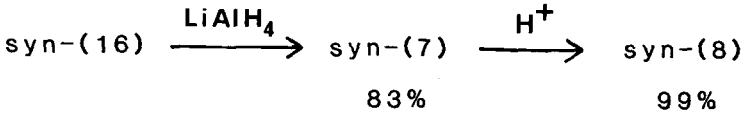


syn-(13) 88% syn-(14) E-syn-(15) 79%

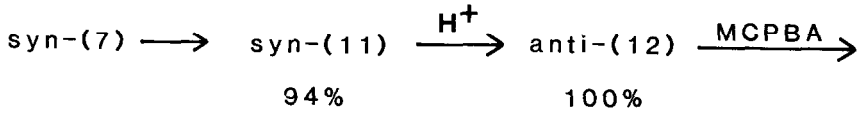
The syn aldol was prepared from the zirconium enolate[2,13] of methyl propionate, the 2.3:1 mixture of aldols (16) being separated by column chromatography. Reduction of the minor isomer (J_{AB} 1.8 Hz, δ_{Me} 17.97 p.p.m.) gave anti-(7), so the major isomer (J_{AB} 5.6 Hz, δ_{Me} 14.15 p.p.m.) must be syn. The same reactions as before gave single and different isomers of the lactone (6), the tetrahydrofuran (8) and the allylic sulphide (12). Oxidation and rearrangement of the syn allylic sulphide (12) gave a single and different isomer of the allylic alcohol (15) which we deduce is the E-anti-isomer.[11]



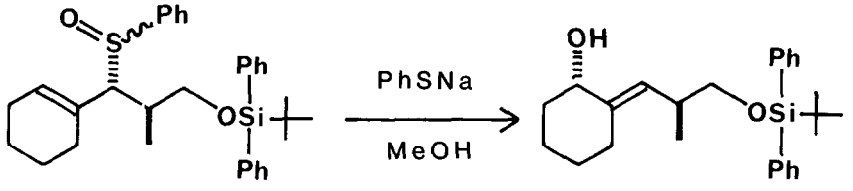
syn-(16) 59% anti-(17) 65% 31%



83% 99%



94% 100%



anti-(13) 89% E-anti-(15) 76%

Table: Assignment of Stereochemistry

Compound	(4)	(16)	(7)	(11)	(6)	(8)	(5/17)	(12)
Anti J_{AB} (Hz)	2.3	1.8	4.9	3.4	8.9	10.4	11.6	9.9
Syn J_{AB} (Hz)	-	5.6	5.4	2.4	12.2	8.2	11.1	9.5
Anti δ_{Me} (ppm)	16.70	17.97	18.45	18.91	13.82	16.70	-	15.95
Syn δ_{Me} (ppm)	-	14.15	11.79	11.99	13.69	15.36		15.59

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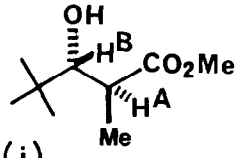
6. Though coupling constants (J_{AB}) are characteristic for aldols from t-alkyl aldehydes (e.g. i),[5] the ^{13}C NMR, particularly δ_{Me}, is more reliable: δ_{Me} (anti) 12-18 p.p.m.; δ_{Me} (syn) 9-13 p.p.m. (ref 7).



(i)

J_{AB} 3 Hz

δ_{Me} 16.6 p.p.m.

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11. Syn and anti (15) are indistinguishable by ^1H or ^{13}C NMR (thus confirming the E configuration of the double bond) but their 2,4-dinitrobenzoates show small differences in their ^1H NMR spectra. Both silylated alcohols (15) have δ 5.09(1H, d, J 9.3, CHOH), 4.05(1H, m, OH), 3.48(2H, m, CH_2OSi), 2.65(1H, m, CHMe), 1.06(9H, s, Bu^t), and 1.01(3H, d, J 6.7, CHMe); the 3,5-dinitrobenzoates have: syn isomer, δ 5.52(1H, m, CHOCOR), 5.31(1H, d, J 8.0 Hz, CH=), 3.48(2H, d, J 6.3 Hz, CH_2OSi), 2.67(1H, m, CHMe), 1.03(9H, s, Bu^t), and 1.08(3H, d, J 6.3, CHMe); anti isomer δ5.57(1H, m, CHOCOR), 5.30(1H, d, J 9.2 Hz, CH=), 3.48 and 3.44(2H, ABX_2, J_{AB} 9.8, J_{AX} 9.8, J_{BX} 6.6 Hz, diastereotopic CH_2OSi), 2.67(1H, m, CHMe), 0.97(3H, d, J 6.7 Hz, CHMe), 0.94 (9H, s, Bu^t), and signals for Ar and $(CH_2)_4$.
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