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SYNTHESIS OF COMPOUNDS WITH 1,4-RELATED CHIRAL CENTRES BY PHENYLTHIO MIGRATION: SYN AND ANTI-E-2,4-DIMETHYLHEX-3-ENE-1,5-DIOL

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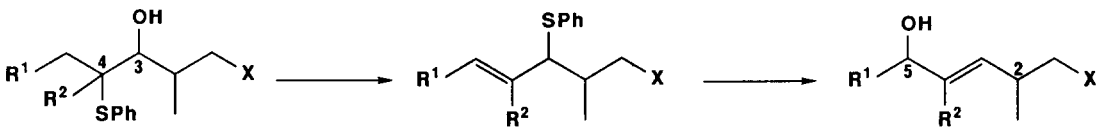
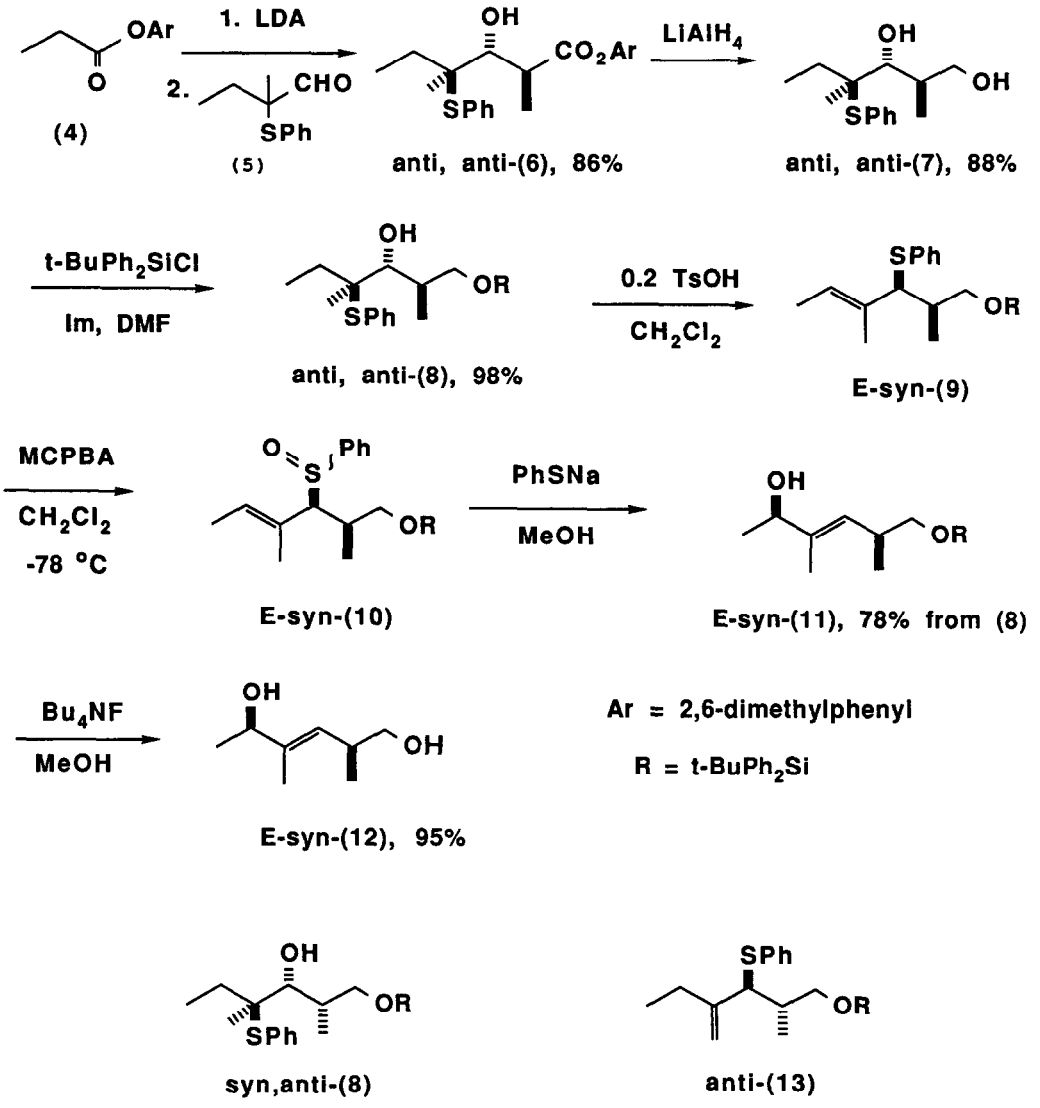
The aldol product from an α-PhS aldehyde, formed with high Cram and anti (aldol) selectivity, was transformed by PhS migration into the syn title compound: the anti compound was made by a Claisen-Ireland rearrangement.

We have shown[1] that phenylthio (PhS) migration in the rearrangement of one series of β-PhS alcohols [**1**; $R^1R^2=(CH_2)_3$] is stereospecific [with inversion at the migration terminus, C-3 of (**1**)] and that the products may be transformed into compounds (**3**) with two chiral centres [C-2 and C-5 in (**3**)] 1,4-related across an E double bond. We now describe our attempts to extend the scope of this work into open-chain compounds [**1**; R^1R^2 not $(CH_2)_n$]. This requires the stereocontrolled formation of a third chiral centre, C-4 in (**1**), and regio- and stereo-control in the formation of a double bond in the rearrangement product (**2**). We describe the synthesis of pure samples of syn and anti-E-2,4-dimethylhex-3-ene-1,5-diol (**12**) in high yield by different routes as an illustration of the methods.

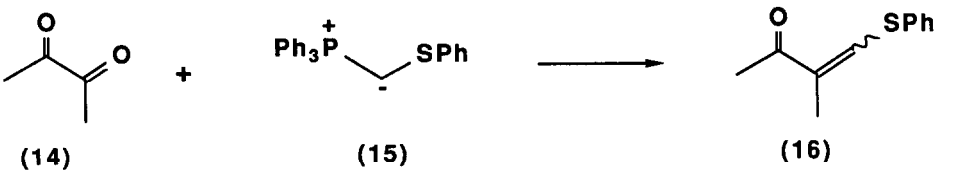


(**1**) (**2**) (**3**)

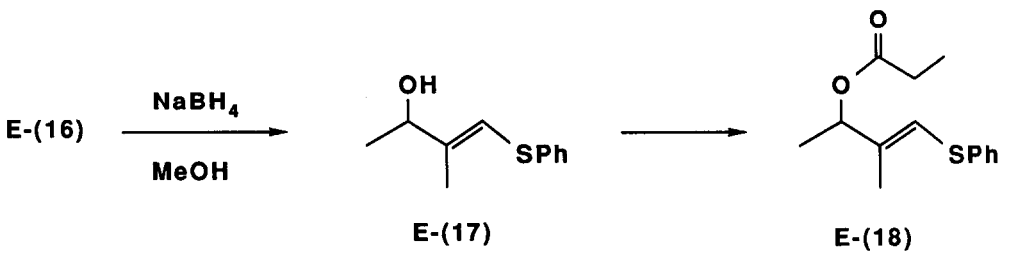
A stereo-controlled aldol reaction[2] gave the pure crystalline hydroxy-ester anti,anti-(**6**)[3] in 86% yield.[5] H.p.l.c. on the crude reaction mixture revealed that the 2,3 (aldol) anti selectivity was complete and that the 3,4 (Felkin[6]) selectivity was 10:1 anti:syn. Reduction and protection gave the β-PhS alcohol (**8**) which gave ($TsOH/CH_2Cl_2$) a mixture[7] of rearranged products containing 85% of E-syn-(**9**). This mixture was not separated but was oxidised (MCPBA in the same solvent) to a mixture of sulphoxides and hence, by the [2,3] sigmatropic Evans-Mislow rearrangement,[8] to the allylic alcohol (**11**). Pure oily E-syn-(**12**) was isolated in 78% yield from anti,anti-(**8**). The syn,anti isomer[5] of (**8**) was made from the boron enolate[9] of EtCOSPh but rearrangement gave an inseparable mixture[7] of 50% E-anti-(**9**), 25% Z-anti-(**9**), and 25% anti-(**13**) so an alternative route to E-anti-(**12**) was sought.



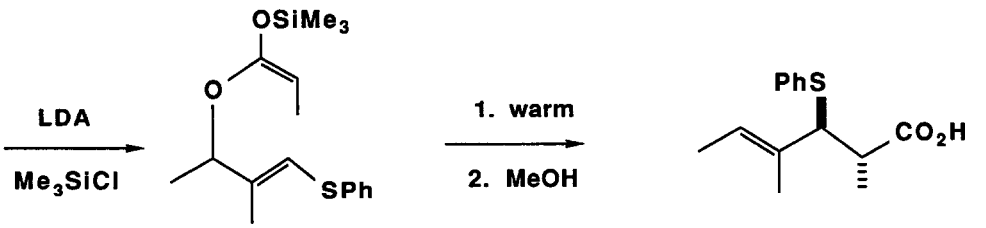
A Wittig reaction between the α-diketone (**14**) and the PhS-ylid[10] (**15**) gave a 50:50 mixture of E and Z-(**16**) which could be equilibrated with PhSH and separated by chromatography to give pure E-(**16**) in 85% yield. Reduction and esterification gave the propionate ester E-(**18**) and hence, by the Claisen-Ireland[11] [3,3] sigmatropic rearrangement on E,E-(**19**), E,anti-(**20**) in 73% yield from (**16**), as an 8:1 mixture with the E,syn isomer. Reduction to E,anti-(**9**;R=H), oxidation ($NaIO_4$, MeOH, H_2O, 2 days) and Evans-Mislow[8] rearrangement gave pure crystalline E,anti-(**12**) in 57% yield. The two isomers of (**12**) had different n.m.r. spectra. We propose that these methods will provide general stereocontrolled syntheses of compounds of this type.



(14) (15) (16)

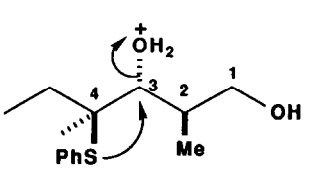


E-(16) E-(17) E-(18)

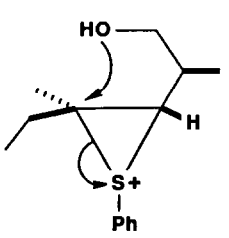


E,E-(19) E-anti-(20)

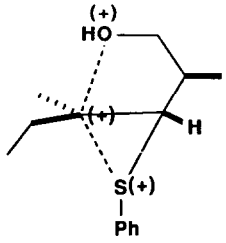
Acid catalysed rearrangement of the unprotected diol anti,anti-(7) gave the tetrahydrofuran (24a) in 98% yield with inversion[5] at both C-3 and C-4. In the opening of the episulphonium ion (22) the alignment of OH and S^+ cannot be 180° about C-4 and the transition state presumable resembles a solvated cation (23). The major diol from the boron enolate route, syn,anti-(7) rearranged in acid to give the epimeric tetrahydrofuran (24b) also with inversion at C-3 and C-4 again in 98% yield.



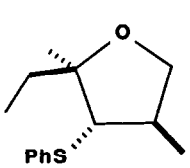
anti,anti-(21)



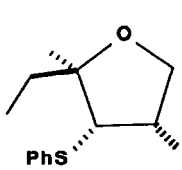
(22)



(23)



(24a)



(24b)

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References and Notes

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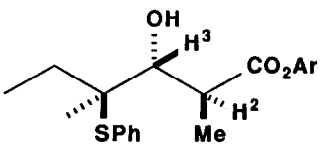
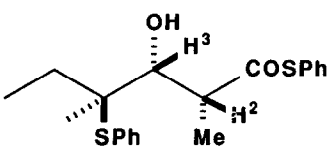
2. C.H. Heathcock, M.C. Pirrung, S.H. Montgomery, and J. Lampe, Tetrahedron, 1981, **37**, 4087.
3. The syn and anti convention suggested by Masamune[4] is used. The first syn or anti describes the 2,3 stereochemistry and the second describes the 3,4 stereochemistry.
4. S. Masamune, S.A. Ali, D.L. Snitman, and D.S. Garvey, Angew. Chem., Int. Ed. Engl., 1980, **19**, 557; S. Masamune, W. Choy, J.S. Petersen, and L.R. Sita, ibid., 1985, **24**, 1.
5. Both anti aldols, anti,anti-(**6**) and anti,syn-(**6**), had $J_{2,3}$ ca. 3 Hz and δ_{Me} ca. 17 p.p.m., whereas both syn aldols, syn,anti-(**25**) and syn,syn-(**25**), had $J_{2,3}$ 5.3 Hz and δ_{Me} ca. 15 p.p.m., in agreement with previous work.[1] The stereochemistry of the tetrahydrofuran (**23a**) was determined by n.O.e. experiments: that of (**23b**) could not be so determined because of overlapping signals in its ^{1}H n.m.r. spectrum.



anti,anti-(6)



syn,anti-(25)

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7. The difference in stereo- (E vs. Z **9**) and regio- (**9** vs. **13**) selectivity in the rearrangement of anti,anti-(**8**) and syn,anti-(**8**), two diastereoisomers which differ only at a chiral centre not involved in the rearrangement (C-2) is remarkable. Molecular mechanics calculations suggest that the chiral sulphur atom in the episulphonium ion intermediate may transmit this stereochemical information.
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