An Effective Method for Controlling 3,4-Stereochemistry of Aldols. Direct Preparation of Optically Active 2,3-*anti*-3-Hydroxy-2-methyl Carbonyl Compounds[1]

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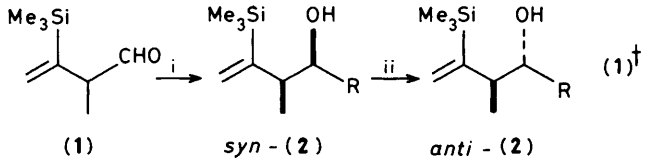
Both 3,4-*syn*- and 3,4-*anti*-aldols can be prepared selectively from 2-methyl-3-trimethylsilylalk-3-enyl carbonyl compounds *via* 1,2-asymmetric induction; thus optically active 2,3-*anti*-3-hydroxy-2-methyl carbonyl compounds can be prepared by the reaction of optically active (*R*)-2-methyl-3-trimethylsilylbut-3-enal (**1**) with the lithium enolate of 2,6-di-t-butyl-4-methylphenyl propionate.

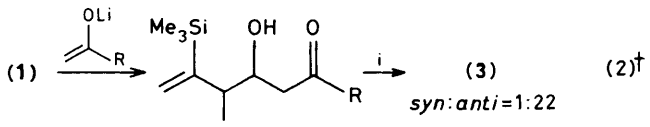
Diastereoselective addition of enolate anions to chiral aldehydes has attracted much interest in recent years. The methods that have been developed for dealing with this 'Cram's rule problem' are double diastereodifferentiation[2] and Lewis acid mediated additions of enolsilanes to chiral aldehydes.[3]

Recently, we reported that 2-methyl-3-trimethylsilylbut-3-enal (**1**) reacts with Grignard reagents highly selectively to afford 'Cram products' *e.g.* *syn*-(**2**), and that *syn*-(**2**) thus prepared can be readily converted into their diastereoisomers, *anti*-(**2**), *via* oxidation and subsequent reduction with $NaBH_4$ [equation (1)].[4] In this communication we report that (**1**) also reacts with ester or ketone enolate anions with high diastereofacial preference, and that this reaction provides a direct method for preparation of optically active 2,3-*anti*-3-hydroxy-2-methyl carbonyl compounds.

Condensation of racemic (**1**) with the lithium enolate of ethyl acetate in tetrahydrofuran (THF) (−78 °C, 20 min). gave an 8:1 diastereoisomeric ratio of *syn*- to *anti*-addition product (**3**), as determined by ^1H n.m.r. spectroscopy (200 MHz). Oxidation of the diastereoisomeric mixture of (**3**) with pyridinium chlorochromate (PCC) and subsequent reduction with $NaBH_4$ furnished *syn*- and *anti*-(**3**) in a ratio of 1:22 [equation (2)].‡ Similarly, reaction of (**1**) with the lithium enolate of acetone (THF, −78 °C, 15 min) afforded predominantly *syn*-(**4**) [equation (2)].‡ The *anti*-isomer of (**4**)‡ was prepared highly selectively by the procedure shown in equation (3). Reaction of (**1**) with allylmagnesium bromide afforded addition product (**5**) (*syn*:*anti* 3:1); the diastereoselectivity observed in this reaction is much lower than in the reaction with alkyl Grignard reagents.[4] Oxidation of the diastereoisomeric mixture of (**5**) with PCC followed by reduction of the resulting ketone with $NaBH_4$ afforded *anti*-(**5**) with >98% diastereoselectivity; subsequent Wacker oxidation yielded *anti*-(**4**).[5]

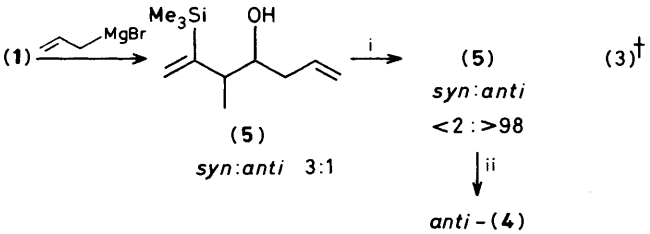


Reagents: i, RMgBr; ii, CrO_3 then $NaBH_4$.



(**3**); R = OEt
syn:*anti* 8:1

(**4**); R = Me
syn:*anti* 9:1

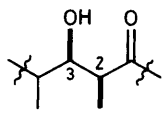


Reagents: i, PCC then $NaBH_4$; ii, O_2, $PdCl_2$.

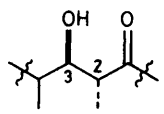
Various enolate anions which give either 2,3-*syn*- or 2,3-*anti*-aldols by reaction with aldehydes have been reported;[6] the reaction of (**1**) with these reagents should provide a convenient method of controlling three consecutive chiral centres in acyclic compounds.[7] Although double diastereodifferentiation provides a direct method for the preparation of optically active 2,3-*syn*-3-hydroxy-2,4-dimethyl carbonyl compounds [2,3-*syn*-(**6**)], synthesis of optically active 2,3-*anti*-(**6**) requires an indirect route,[2,8,9] direct methods being only partially successful.

Thus, the reaction of (*R*)-(**1**)[4] with the lithium enolate of 2,6-di-t-butyl-4-methylphenyl propionate (BHT propionate)[10] was carried out with the aim of preparing optically active 2,3-*anti*-(**6**).

Reaction of (*R*)-(**1**) with the lithium enolate of BHT propionate in THF (−78 °C, 2 min) followed by treatment of the crude product (**7**)§ with $LiAlH_4$ afforded the diol (**8**)



2,3-*syn*-(**6**)

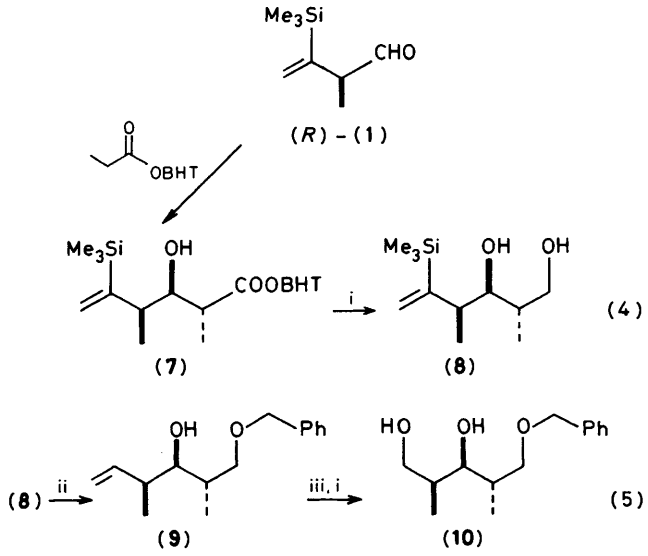


2,3-*anti*-(**6**)

† Although only one enantiomer is depicted, all structures represent racemic mixtures.

‡ The ^1H n.m.r. data (solvent): *syn*-(**3**) (CCl_4 + D_2O) δ 0.06 (s, 9H), 1.10 (d, *J* 7 Hz, 3H), 1.21 (t, *J* 8 Hz, 3H), 1.94—2.53 (m, 3H), 3.80 (dt, *J* 3, 9 Hz, 1H), 4.05 (q, *J* 8 Hz, 2H), 5.37 (d, *J* 2.4 Hz, 1H), and 5.57 (d, *J* 2.4 Hz, 1H). *anti*-(**3**) (CCl_4 + D_2O) δ 0.06 (s, 9H), 0.94 (d, *J* 7 Hz, 3H), 1.17 (t, *J* 8 Hz, 3H), 2.16—2.57 (m, 3H), 3.76—4.03 (m, 1H), 4.04 (q, *J* 8 Hz, 2H), 5.40 (d, *J* 2.4 Hz, 1H), and 5.64 (d, *J* 2.4 Hz, 1H). *syn*-(**4**) (CCl_4 + D_2O) δ 0.05 (s, 9H), 0.99 (d, *J* 7 Hz, 3H), 2.03 (s, 3H), 2.10—2.63 (m, 3H), 3.86 (dt, *J* 4, 8 Hz, 1H), 5.36 (d, *J* 2.4 Hz, 1H), and 5.56 (d, *J* 2.4 Hz, 1H). *anti*-(**4**) (CCl_4 + D_2O) δ 0.09 (s, 9H), 0.95 (d, *J* 7 Hz, 3H), 2.06 (s, 3H), 2.20—2.60 (m, 3H), 3.95 (q, *J* 6 Hz, 1H), 5.41 (d, *J* 3 Hz, 1H), and 5.64 (d, *J* 3 Hz, 1H). *anti*-(**5**) δ 0.08 (s, 9H), 0.95 (d, *J* 7 Hz, 3H), 1.46 (br s, 1H), 1.80—2.51 (m, 3H), 3.48 (dt, *J* 3.5, 8 Hz, 1H), 4.80—5.12 (m, 2H), 5.42 (d, *J* 2.4 Hz, 1H), 5.63 (d, *J* 2.4 Hz, 1H), and 5.50—6.10 (m, 1H).

§ Although the product (**7**) could be separated from excess of BHT propionate by preparative chromatography on silica gel, purification was simpler after the formation of (**8**).



BHT = 2,6-di-t-butyl-4-methylphenyl

Reagents: i, $LiAlH_4$; ii, $PhCH_2Br$, NaH, then NaH, hexamethylphosphoramide; iii, O_3.

$\{[\alpha]_D^{25}$ −18.5° (*c* 1.00, $CHCl_3$)} in 70% yield along with *ca.* 3% of an unidentified product¶ [equation (4)]. The ^1H and ^{13}C n.m.r. spectra showed (**8**) to be homogeneous.** The structure (**8**), tentatively assigned on the basis of the high 'Cram' product selectivity of the reaction of (**1**) with nucleophiles, was confirmed by transformation of (**8**), *via* (**9**), into the known compound (**10**)†† $\{[\alpha]_D^{25}$ +36.2° (*c* 0.90, $CHCl_3$), (lit.[7d] $[\alpha]_D$ +38.4°)} as shown in equation (5).

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¶ Very high diastereoselectivity is observed in this reaction compared to the reaction with acetone or the acetate enolate anion; however, ethyl carbonyl compounds exhibit a higher diastereoselectivity than the corresponding methyl carbonyl compounds (ref. 11).

** (**8**): ^1H N.m.r. (CCl_4 + D_2O) δ 0.08 (s, 9H), 0.85 and 0.98 (2d, *J* 7 Hz, 6H), 1.50—1.90 (m, 1H), 2.40—2.73 (m, 1H), 3.30 (dd, *J* 3.5, 8 Hz, 1H), 3.40—3.70 (m, 2H), 5.45 (d, *J* 3 Hz, 1H), and 5.65 (m, 1H); ^{13}C n.m.r. ($CDCl_3$) δ 1.2, 12.1, 13.7, 36.7, 40.1, 67.2, 77.0, 125.3, and 155.1.

†† (**10**): ^{13}C n.m.r. ($CDCl_3$) δ 8.8, 13.2, 36.0, 36.5, 67.3, 73.5, 76.2, 78.5, 127.6, 127.8, 128.4, and 137.6.

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