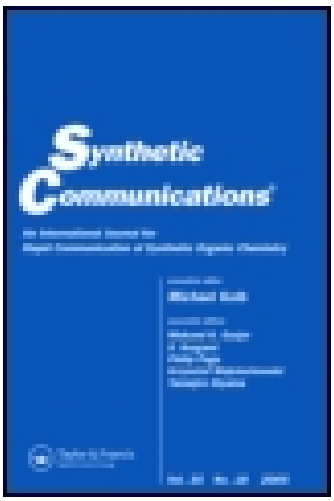

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CHEMISTRY OF ETHANEDIYL S,S-ACETALS 9[§]-ASYMMETRIC SYNTHESIS OF CHIRAL *CIS* ALLYLIC ALCOHOLS

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Abstract: *(2Z,1S)*-1,3-diphenyl-2-propenol (**3**) is obtained from the chiral 5,6-dihydro-1,4-dithiin **1b** in two steps and 60% enantiomeric excess. Combining our previously reported stereoselective double bond formation and this 1,4 asymmetric induction introduces a new route to chiral allylic alcohols with *cis* geometry from simple aldehydes and methyl ketones.

In a recent paper[1] we reported a new synthetic strategy that enables the stereoselective preparation of *cis* allylic alcohols. This is based on the coupling of lithiated 5,6-dihydro-1,4-dithiins like **1a** [that are readily available[2] from ethanediyl *S,S*-acetal (1,3-dithiolane) derivatives of either aldehydes or methyl ketones] with aldehydes, in anhydrous tetrahydrofuran at -78° C, using $Ti(OPr^i)_4$ as catalyst. The entire process, including the stereoselective removal[3] of the disulfur bridge

§ Part 8 in the same series: Ref. 3.

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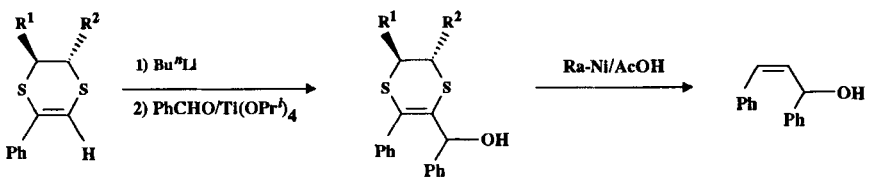
from the coupling product, is depicted below:



1 2 3

a) $R^1 = R^2 = H$; b) $R^1 = R^2 = CH_3$

We have now found that optically active 5,6-dihydro-1,4-dithiins like **1b** can be coupled with prochiral aldehydes to afford their corresponding C-3 substituted derivatives **2b** [and, more interestingly, the related allylic alcohols, after stereoselective sulfur removal[3]] with a significant diastereomeric excess accounted for by a rather uncommon 1,4 asymmetric induction.

The starting 5*S*,6*S*-dimethyl-2-phenyl-5,6-dihydro-1,4-dithiin (**1b**), $[\alpha]_D^{21}$ = -18.0° was smoothly prepared[2] from 2-phenyl-2,4*S*,5*S*-trimethyl-1,3-dithiolane[4], $[\alpha]_D^{21}$ = -24.0°, obtained[5] from methyl phenyl ketone and the specially synthesized[6] 2*S*,3*S*-butanedithiol (L-*threo*-butanedithiol). Treatment[1] of **1b** with Bu^{n}Li and then benzaldehyde in the presence of Ti(OPr^i)$_4$ afforded **2b**, as a diastereomer mixture, the stereoselective desulfurization[3] of which eventually led to the *cis* 1,3-diphenyl-2-propenol (**3**) with 60% (*S*)-enantiomer excess. This excess was determined by both ^{1}H NMR analysis of the diastereomeric (*S*,*S*,*R*)-**2b** and (*S*,*S*,*S*)-**2b** mixture (see below), and full hydrogenation of the latter that afforded an enantiomeric mixture of the already known[7,8] 1,3-diphenyl-1-propanol.

Ti^{IV} has been reported[9,10] to coordinate sulfur and carbonyl oxygen atoms by forming five membered rings. This may account for the rather unusual 1,4 asymmetric induction observed here, if one considers the formation of two distinct

diastereomeric cyclic transition states including the aldehyde carbonyl group, the carbanionic dithiin carbon, its alpha sulfur, and titanium (IV) atoms.

In spite of a somewhat difficult preparation[6] of the chiral auxiliary, L-*threo*-butanedithiol, in our opinion these preliminary results do represent the embryo of a useful synthetic strategy for obtaining chiral *cis* allylic alcohols in only few steps starting from simple carbonyl compounds.

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled under N_2 from $LiAlH_4$. GC-MS analyses were performed on a Hewlett-Packard 5980 GS/5971 MS instrument. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. ^1H NMR spectra were recorded on a Bruker WH (270 MHz) instrument in $CDCl_3$ solutions.

2-Phenyl-2,4S,5S-trimethyl-1,3-dithiolane. To a magnetically stirred solution of methyl phenyl ketone (10.0 mmol) in glacial acetic acid (6.0 cm^3), (2*S*,3*S*)-butanedithiol[6] (12.0 mmol) and *p*-toluenesulfonic acid (1.0 mmol) are added in sequence. After 30 min at room temperature the mixture is treated with 10% aq $NaHCO_3$ (100 cm^3) and extracted with Et_2O (3 x 100 cm^3). The combined organic layers are washed with water until neutral, dried (Na_2SO_4), and evaporated *in vacuo*. Chromatography (silica gel; *n*-hexane) of the crude residue affords the title 1,3-dithiolane as an oily C-2 diastereomer mixture (9.0 mmol; 90% yield); $[\alpha]_D^{21} = -24.1°$ (c 1.0, $CHCl_3$). ^1H NMR: δ 1.35 (*d*, 3H, J = 7.1 Hz, CH_3), 1.37 (*d*, 3H, J = 7.1 Hz, CH_3), 2.14 (*s*, 3H, CH_3), 3.46 (*m*, 1H, CH-Me), 3.61 (*m*, 1H, CH-Me), 7.25 (*m*, 3H, aromatic Hs), 7.75 (*m*, 2H, aromatic Hs).

5S,6S-dimetil-2-phenyl-5,6-dihydro-1,4-dithiin (1b). To a solution of 2-phenyl-2,4*S*,5*S*-trimethyl-1,3-dithiolane (1.0 mmol) in anhydrous $CHCl_3$ (50 cm^3), dry Br_2 (1.1 mmol) in the same solvent (10 cm^3) is added dropwise over 10 min, at room temperature and under magnetic stirring. After 25 min (GC-MS monitoring) solid $NaHCO_3$ (2.0 g) and then H_2O (30 cm^3) are added to the reaction mixture. The organic layer is washed with water until neutral, dried (Na_2SO_4), and evaporated *in vacuo* to afford an oily residue that by flash chromatography on silica gel (light pet.) gives the pure oily 5,6-dihydro-1,4-dithiin **1b** (0.8 mmol; 80% yield); $[\alpha]_D^{21}$ = -18.0° (c 1.0, $CHCl_3$). ^1H NMR: δ 1.51 (*d*, 6H, *J*= 6.8 Hz, 2 CH_3), 3.15 (*m*, 2H, 2 CH), 6.42 (*s*, 1H, vinylic H), 7.32 (*m*, 3H, aromatic Hs), 7.56 (*m*, 2H, aromatic Hs).

Preparation of 3. To a solution of pure chiral dithiin **1b** (0.6 mmol) in anhydrous THF (5 cm^3), 1.6 M Bu^{n}Li in *n*-hexane (0.37 cm^3; 0.6 mmol) is added dropwise *via* cannula over 10 min at -78° C, under magnetic stirring and dry argon (or nitrogen) atmosphere. After 20 min a solution of freshly distilled benzaldehyde (0.6 mmol) and $Ti(OPr^i)_4$ (0.1 mmol) in the same solvent (5 cm^3) is also added dropwise *via* cannula. The temperature is kept at -78° C for 15 min and then let to raise to room temperature. After 30 min (GC-MS monitoring) the reaction mixture is treated carefully with 10% aq NH_4Cl (15 cm^3) and extracted with Et_2O (3 x 100 cm^3). The combined organic layers are washed with water until neutral, dried (Na_2SO_4), and evaporated *in vacuo*. Chromatography (silica gel; 8:2 light pet.:Et_2O) of the crude residue affords an oily mixture of diastereomeric (*S*,*S*,*R*)-**2b** and (*S*,*S*,*S*)-**2b** (96% yield); $[\alpha]_D^{21}$ = -35.0° (c 1.0, CH_2Cl_2); IR: 3450 cm^{-1} (broad, $CHCl_3$); ^1H NMR: δ 1.25 (*d*, 3H, *J* = 7.0 Hz, CH_3), 1.32 (*d*, 3H, *J* = 7.0 Hz, CH_3), 3.04 (*m*, 1H, CH-Me), 3.25 (*m*, 1H, CH-Me), 5.42 (*s*, 0.2H, O-CH),

5.63 (*s*, 0.8H, O-CH), 7.30 (*m*, 10H, aromatic Hs). [60% d.e. is deduced from the areas of the peaks at δ 5.42 and 5.63.] The mixture (0.5 mmol) is then treated[3] with Raney nickel W2 (1.5 g, wet) in glacial acetic acid (10 cm^3) for 10 min. Usual work up and purification by filtration on silica gel affords the mixture of *cis* enantiomeric allylic alcohols **3** in 88% yield; $[\alpha]_D^{21}$ = -15.3° (c 1.2, CH_2Cl_2); IR: 3452 cm^{-1} (broad, $CHCl_3$); ^1H NMR: δ 5.66 (*dd*, 1H, $J_{2,1}$= 9.0 Hz, $J_{2,3}$= 11.0 Hz, H-2), 5.72 (*d*, 1H, $J_{1,2}$= 9.0 Hz, H-1), 6.55 (*d*, 1H, $J_{3,2}$= 11.0 Hz, H-3), 7.20-7.42 (*m*, 10H, aromatic Hs).

Overreductive desulfurization of 2b: 1,3-diphenyl-1-propanol. To a suspension of Raney nickel W2 (2.4 g, wet) in dioxane (10 cm^3), a solution of **2b** diastereomer mixture (1.0 mmol) in the same solvent (15 cm^3) is added dropwise at room temperature and under magnetic stirring. After 1 h (GC-MS monitoring) the catalyst is filtered off and the solution shaked with Et_2O (50 cm^3) and H_2O (40 cm^3). The organic layer, dried (Na_2SO_4) and evaporated *in vacuo*, affords after purification on silica gel (*n*-hexane) the enantiomer mixture of (*R*)- and (*S*)-1,3-diphenyl-1-propanol (0.9 mmol; 90% yield); m.p. 42-43° C (*n*-hexane); $[\alpha]_D^{21}$ = -17.3° (c 1.0, CH_2Cl_2) [lit.[7,8] $[\alpha]_D^{21}$ = 28.8° (c 1.0, CH_2Cl_2) for the pure (*R*)-enantiomer; 60% calculated (*S*)-enantiomer excess]; IR and ^1H NMR spectra were identical with those of a racemic 1,3-diphenyl-1-propanol[1,3].

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