LITHIATION OF Δ^2-THIAZOLINES: THE C^2-ANION APPROACH TO 2-SUBSTITUTED DERIVATIVES AND THEIR REACTIVITY

Giancarlo Fantin, Marco Fogagnolo, Alessandro Medici*, and Paola Pedrini

Dipartimento di Chimica, Università di Ferrara, 44100 Ferrara, Italy

Abstract - Lithiation of 2-unsubstituted Δ^2-thiazolines and quenching with various electrophiles to 2-funcitonalized derivatives is reported. In particular quenching of thiazolines (**1a** and **1b**) with trimethylsilyl chloride affords the corresponding 2-trimethylsilyl-Δ^2-thiazolines (**7a** and **7b**). The reactivity of these masked C^2-anions toward electrophiles is described. Similar approach is developped for chiral 4-[(*tert*-butyldimethylsilyloxy)methyl]-2-thiazoline (**12**). The synthesis of the chiral 2-formyl derivative, generated *in situ* from the C^2-anion and *N*-formylmorpholine, and its reactivity toward phosphonium salt are also discussed.

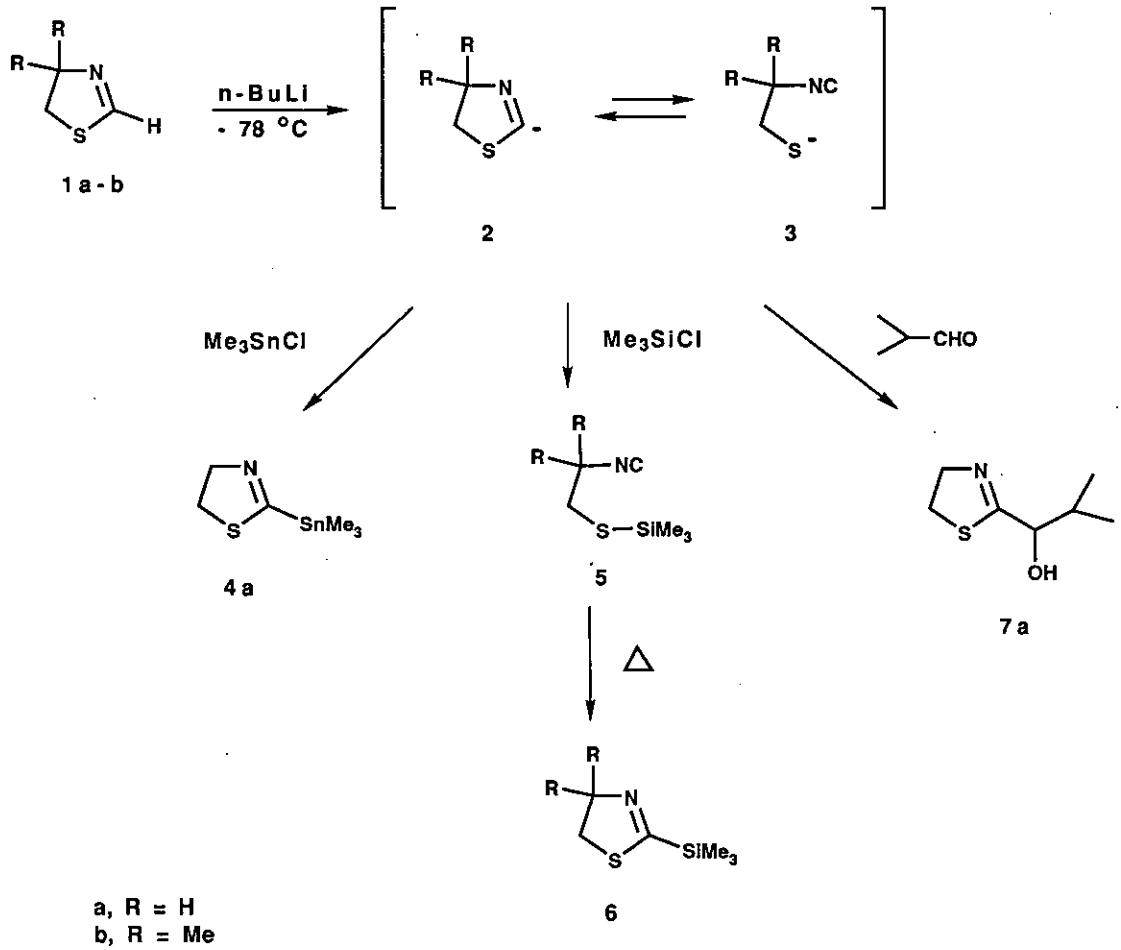
In previous paper we described the synthetic utility of lithiation of 2*H*-thiazoles[1] and 2*H*-oxazoles[2] that by reaction of the C^2-anion with trimethylsilyl and trimethyltin chloride afforded the trimethylsilyl and trimethylstannyl derivatives. These metallated compounds, that can be viewed as masked C_2-anion, have shown their versatility to obtain new carbon-carbon bond at C^2-position.[3] Similar approach has been extended to 2-oxazolines that gave after lithiation and quenching with the same electrophiles, the expected stannyl derivative but failed in obtaining of the silyl compound.[4] We have also reported the synthesis of 2-trimethylsilyl- and 2-trimethylstannyl-2-thiazolines and their reactivity toward various electrophiles.[5] Herein we describe a full account of the synthesis of metallated thiazolines, also with chiral substituents, and of their potential in obtaining 2-substituted derivatives.

Results and Discussion

Lithiation of thiazolines (**1a** and **1b**) with *n*-BuLi in ether produces an equilibrium mixture of the C^2-anion (**2**) and the open-chain β-isocyano thiolate (**3**) (Scheme 1). A similar behaviour has been previously reported for Δ^2-oxazolines and oxazoles under the identical experimental conditions,[2,4] and the species in equilibrium can be trapped by appropriate electrophiles. 2-(Trimethylstannyl)-2-thiazoline (**4a**) and 2-(hydroxyisobutyl)-2-thiazoline (**7a**) were obtained by quenching the equilibrium mixture with 1 equivalent of trimethyltin chloride or 2 equivalents of isobutyraldehyde respectively. On the other hand, the open-chain β-isocyanothiolates (**3**) were trapped with 1 equivalent of trimethylsilyl chloride as silyl thio ethers (**5**). Distillation of **5** in oil bath at 120 °C gave satisfactory yields of the 2-trimethylsilylthiazolines (**6a**) and (**6b**) respectively (Scheme 1). The same procedure, i.e. the thermal conversion of the silyl isocyanide into the silylazole, has been succesfully applied in the preparation of 2-trimethylsilyloxazoles but it was unfeasible with Δ^2-oxazolines.[4] Although this isomerization should be disfavoured

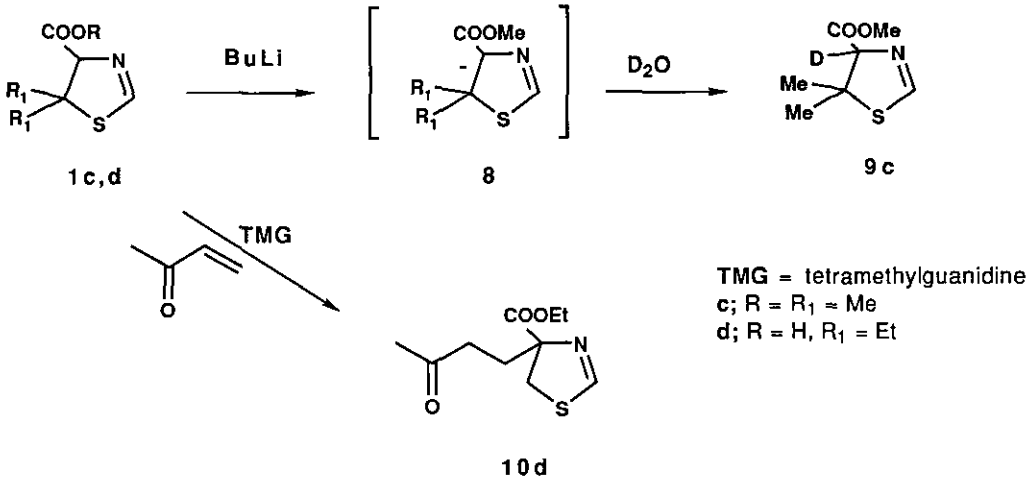
in both cases due to the relative O-Si vs. C-Si bond strengths, the cyclization to 2-(trimethylsilyl)oxazoles appears to be assisted by the aromaticity.[3] In our case, however, the absence of the aromaticity in the resulting product is balanced by the easier insertion of the isonitrile into the S-Si bond.[3,4]

Scheme 1



The possibility of obtaining through the C^2-anion various 2-substituted thiazolines by reaction with different electrophiles, led us to apply this methodology to chiral Δ^2-thiazolines. Lithiation of *D*-4-carbomethoxy-5,5-dimethyl-2-thiazoline (**1c**) gave the C^4-anion (**8**) which by quenching with D_2O afforded the deuterated thiazoline (**9c**) in practically quantitative yield. Moreover, 4-carboethoxy-2-thiazoline (**1d**) with catalytic amount of tetramethylguanidine in ethanol gave by treating with methyl vinyl ketone the 4-alkyl derivative (**10d**) (Scheme 2). The highest acidity of the C^4-proton is imputable to the presence of the carboxylate group, so, in order to obtain the C^2-anion, the esteric function has been transformed into the hydroxymethyl group by reduction with sodium borohydride.[6]

Scheme 2



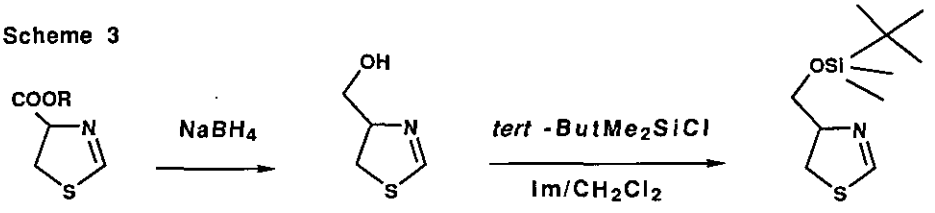
1c,d 8 9c

10d

TMG = tetramethylguanidine
c; R = R_1 = Me
d; R = H, R_1 = Et

Reduction of the racemic 4-carboethoxy- and 4-carbomethoxy-2-thiazolines (**1d** and **1e**) with sodium borohydride in ethanol/water (1/1) at 0° C gave the 4-hydroxymethyl derivative (**11**) (Scheme 3). The hydroxyl group was subsequently protected as *tert*-butyldimethylsilyl derivative (**12**) by reaction with 1 equivalent of *tert*-butyldimethylsilyl chloride since the common methods[7] to obtain the methoxy derivative were unsuccessful probably because of the instability of the O-anion.

Scheme 3

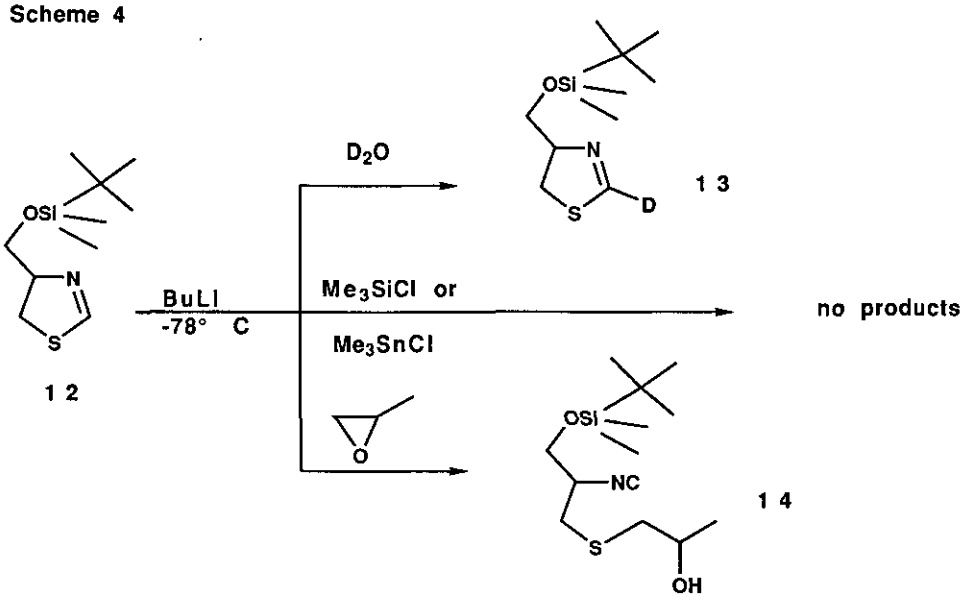


1d,e 11 12

d; R = Et
e; R = Me

Lithiation of the chiral thiazoline (**12**) with *n*-BuLi in ether produced the expected equilibrium mixture of the C^2-anion and the open-chain β-isocyanothiolate, that can be trapped by the appropriate electrophiles. The C^2-anion, quenched with D_2O, afforded the 2-deuterated thiazoline (**13**) in quantitative yield while the open-chain β-isocyano- thiolate, treated with 1.1 equivalent of propylene oxide, gave the thio ether (**14**) in 48% yield (Scheme 4). Surprisingly no 2-trimethylsilyl and 2-trimethylstannyl derivatives were obtained by treating the equilibrium mixture with trimethylsilyl and trimethyltin chloride, respectively.

Scheme 4

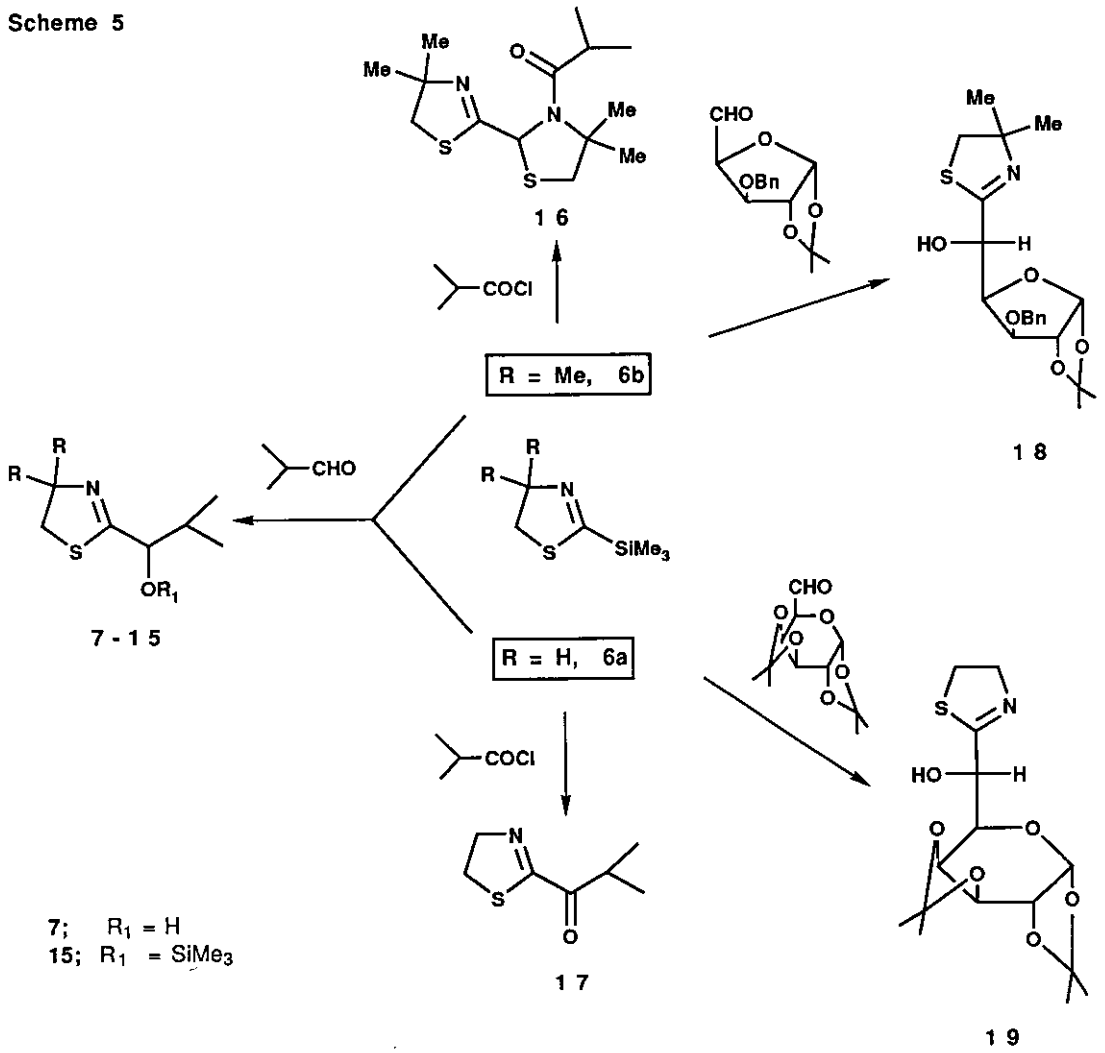


On the basis of this results, we explored the possibility to obtain various 2-substituted thiazolines using 2-trimethylstannyl- and 2-trimethylsilyl derivatives (**4a**) and (**6**) respectively, and the C^2-anion of (**12**) through the reactions with electrophiles.

The reactivity of 2-(trimethylsilyl)-2-thiazolines (**6**) has been examined with two different electrophiles, i.e. aldehydes and acyl chloride, which both gave the 2-thiazoline derivatives by substitution of the $SiMe_3$ group (Scheme 5). The reaction with isobutyraldehyde produced the silyl ethers (**15**) which treated with tetra-*n*-butylammonium fluoride to give the corresponding alcohols (**7**). In order to obtain an asymmetric control we explored the reaction with chiral aldehydes. The reaction of **6a** with the protected *D-galacto*-hexodialdopyranose in benzene afforded the corresponding alcohol (**19**) (50% yield, ds ≥ 95%) and the reaction of **6b** with the protected *D-xylo*-pentodialdofuranose gave the alcohol (**18**) (30% yield, ds = 85%). The stereochemistry at the newly hydroxymethylene center can be assigned on the basis of the results obtained for 2-trimethylsilylthiazole[8] where the stereochemical outcome is in agreement with the non chelate Felkin-Anh model for asymmetric induction.[9] On the other hand, the reaction with isobutyryl chloride gave rise to different adducts depending on the substituents of the thiazoline ring: in particular the silylthiazoline (**6a**) afforded the 2-acyl derivative (**17**) in 50% yield while **6b** produced the addition product (**16**) in 30% yield. A similar behaviour has been detected with 2-trimethylsilylthiazole and ethyl chloroformate.[1]

The reactivity of 2-(trimethylstannyl)-2-thiazoline (**4a**) has been investigated in respect to palladium-catalyzed cross-coupling reaction, methodology recently employed for the arylation of heterocycles. The reaction with 2-bromothiophene and 3-bromoquinoline in the presence of catalytic amounts of $Pd[P(Ph_3)]_4$ resulted in a progressive decomposition of the stannyl derivative without production of the corresponding cross-coupling adduct.

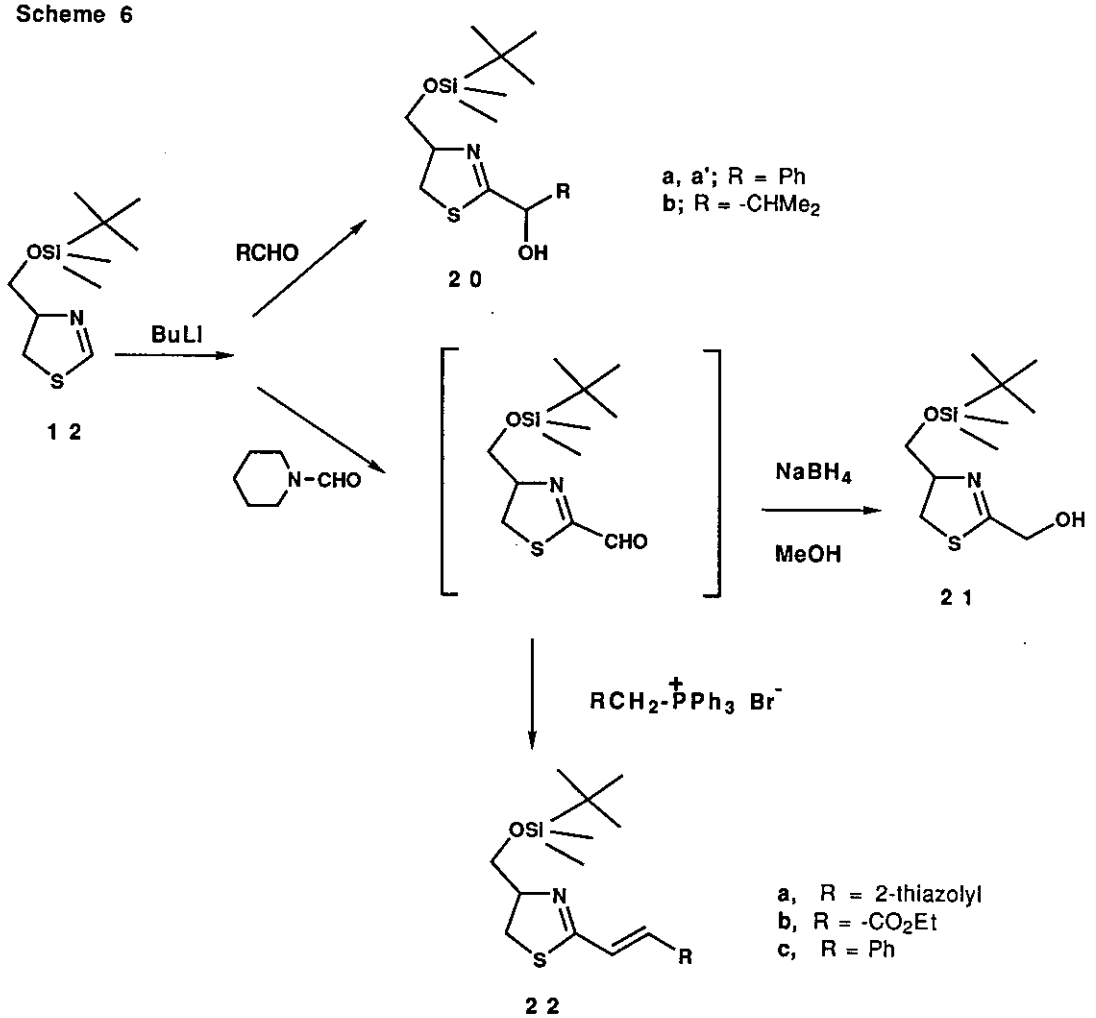
Scheme 5



The synthetic utility of the thiazoline (**12**) was explored by quenching the C^2-anion with aldehydes, also in order to obtaining diastereomeric control. The reaction with isobutyraldehyde (1.5 equivalents) gave only one diastereoisomer of 2-(hydroxyisobutyl)-2-thiazoline (**20b**) but in low yield (10%), while benzaldehyde produced the alcohols (**20a** and **20a'**) in satisfactory yield (45%) but with a 3:1 diastereomeric ratio[10] (Scheme 6). Owing to the importance of functionalizing the C^2-position, the equilibrium mixture was also treated with *N*-formylmorpholine (1.5 equivalents) in order to obtain the 2-formyl derivative. This compound was generated *in situ* but cannot be isolated from the reaction mixture because of its rapid decomposition during the work-up. Its presence, at 0 °C in diethyl ether solution, is indirectly confirmed by treating the crude reaction mixture with sodium borohydride in methanol to obtain the 2-hydroxymethyl derivative (**21**) in 50% yield.

The synthetic potential of the 2-formyl derivative has been further investigated in respect to the Wittig reaction. The addition of the appropriate phosphonium salt to the solution of 2-formyl derivative at 0 °C produced in satisfactory yield the E-alkenes **22** (**22a**, 68%; **22b**, 58%; **22c**, 16%). It is worth mentioning that no further base was added to the reaction mixture to generate the phosphonium ylide. On this basis, the diastereoselective addition to carbon-carbon double bond is under investigation.

Scheme 6



EXPERIMENTAL

^{1}H-Nmr spectra were obtained on 80 MHz WP80 Bruker, on a 200 MHz AC-200 Bruker and on 300 MHz Gemini 300 Varian spectrometers. Chemical shifts were given in parts per million from Me_4Si as internal standard. Ir spectra were recorded on a Perkin Elmer Model 297 grating spectrophotometer. Elemental analyses were performed on a 1106 Microanalyzer (Carlo Erba).

2-Thiazoline (**1a**) *was prepared according to the literature procedure*[11]: bp 139-140°C (lit.[11], bp 139-140°C); ^{1}H-nmr (80 MHz, $CDCl_3$) δ 3.20 (dt, J = 1.0 and 9.0 Hz, 2H), 4.22 (ddt, J = 1.0, 2.4 and 9.0 Hz, 2H), 7.84 (t, J = 2.4 Hz, 1 H).

4,4-Dimethyl-2-thiazoline (**1b**) was prepared in 30% yield by treatment of 4,4-dimethyl-2-oxazoline with P_2S_5 according to the literature[12]: bp 145-148 °C (lit.,[13] 61 °C/45 Torr); ^{1}H-nmr (80 MHz, $CDCl_3$) δ 1.37 (s, 6 H), 3.02 (s, 2 H), 7.67 (s, 1 H). *D*-4-Carbomethoxy-5,5-dimethyl-2-thiazoline (**1c**) was prepared in 40% yield by degradation of Penicillin G methyl ester.[14]

The racemic 4-carboethoxy- and 4-carbomethoxy-Δ^2-*thiazoline* (**1d** *and* **1e**)[15] *were obtained, according to the* Meyers' procedure,[16] from L-cysteine hydrochloride,[17] ethyl or methyl chloroformate and triethylamine in dichloromethane (yield 86% and 88% respectively). 1,2,3,4-di-*O*-Isopropylidene-α-*D-galacto*-hexodialdo-1,5-pyranose[18] and 1,2-*O*-isopropylidene-3-*O*-benzyl-α-*D -xylo* -pentodialdofuranose[19] are prepared as described. All lithiation reactions were carried out under N_2 and with freshly distilled and dried solvents.

Lithiation and quenching of 2-thiazolines (1a and 1b). General procedure. A solution of *n*-BuLi (36 mmol) in *n*-hexane was added dropwise to a cooled (-78 °C) and stirred solution of the selected thiazoline (32 mmol) in ether (40 ml). After 1 h stirring at -78 °C, the reaction mixture was quenched with the appropriete electrophile.

Quenching of **1a** with trimethyltin chloride (6.4 g, 32 mmol) in ether (20 ml) gave, after filtration over Celite and *distillation, 3.5 g (44%) of 2-trimethylstannyl*-2-thiazoline (**4a**): bp 108-110 °C (18 mmHg); ir (film) 1570, 1250, 1190 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 0.37 (s, 9 H), 3.02 (t, J = 9.0 Hz, 2 H), 4.35 (t, J = 9.0 Hz, 2 H). Anal. Calcd for $C_6H_{13}NSSn$: C, 28.83; H, 5.24; N, 5.60. Found: C, 28.95; H, 5.28; N, 5.67.

Quenching of **1a** with isobutyraldehyde (4.6 g, 64 mmol) and workup with aqueous solution of NaCl and anhydrous Na_2SO_4 gave after chromatography (silica gel, *n*-hexane-ether 1:1) 1.37 g (27%) of 2-(hydroxyisobutyl)-2-thiazoline (**7a**): oil; ir (film) 3260 (broad), 1620 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 0.87 (d, J = 12.4 Hz, 3 H), 1.05 (d, J = 12.4 Hz, 3 H), 1.75-2.20 (m, 1 H), 3.37 (t, J = 8.6 Hz, 2 H), 4.05-4.40 (m, 3 H); ms m/z 159 (M^+). Anal. Calcd for $C_7H_{13}NOS$: *C, 52.79; H, 8.23; N, 8.80. Found: C, 52.89; H, 8.25; N, 8.73.*

Quenching of thiazolines **1a** and **1b** with trimethylsilyl chloride (3.5 g, 32 mmol) in ether (30 ml) gave, after filtration over Celite and removing of the solvent, the essentially pure β-isocyanotrimethylsilyl thio ethers **5a** and **5b** (90% by nmr) respectively. Compound (**5a**) showed the following: ir (film) 2120, 1670, 1250 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 0.35 (s, 9 H), 2.75 (br t, J = 7.0 Hz, 2 H), 3.50 (t, J = 7.0 Hz, 2 H). Compound (**5b**): ir (film) 2115, 1675, 1250 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 0.35 (s, 9 H), 1.50 (m, 6 H), 2.70 (m, 2 H). Distillation of the crude **5** in a Fisher apparatus (oil bath 120 °C, 18 mmHg) gave the 2-trimethylsilyl derivatives (**6a**) and (**6b**) in 42% and 53% yield respectively.

2-(Trimethylsilyl)-2-thiazoline (**6a**): bp 86-87 °C (18 mmHg); ir (film) 1570,1250 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 0.27 (s, 9 H), 2.80 (t, J = 9.0 Hz, 2 H), 4.39 (t, J = 9.0 Hz, 2 H). Anal. Calcd for $C_6H_{13}NSSi$: C, 49.07; H, 7.65; *N, 8.17. Found: C, 49.17; H, 7.61;* N, 8.24.

4,4-Dimethyl-2-trimethylsilyl-2-thiazoline (**6b**): bp 95-97 °C (18 mmHg); ir (film) 1570, 1250 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 0.33 (s 9 H), 1.42 (s, 6 H), 2.94 (s, 2 H). Anal. Calcd for $C_8H_{17}NSSi$: C, 51.06; H, 9.11; N, 7.44. Found: C, 51.15; H, 9. 05; N, 7.47.

Lithiation and quenching of thiazoline (1c) with D_2O. Lithiation was carried out as above for **1a** and **1b** starting from the thiazoline (10 mmol) and *n*-BuLi (11 mmol) in ether (20 ml). Quenching of the thiazoline **1c** with D_2O (10 mmol) afforded, after workup with aqueous solution of NaCl, anhydrous Na_2SO_4 and removing of the solvent under reduced pressure, the 4-deuterated derivative **9c** in practically quantitative yield: oil; ^{1}H-nmr (200 MHz, $CDCl_3$) δ 1.37 (s, 3 H), 1.74 (s, 3 H), 3.82 (s, 3 H), 8.14 (s, 1 H).

4-Carboethoxy-4-(3-oxobutyl)-2-thiazoline (10d). A solution of the thiazoline (**1d**) (0.5 g, 3.1 mmol), methyl vinyl ketone (0.21 g, 3.1 mmol) and tetramethylguanidine (35 mg, 0.31 mmol) in ethanol (30 ml) was stirred at room temperature for 3 days. After addition of a saturated solution of NaCl (30 ml), extraction with ether and chromatography (silica gel, petroleum ether-ethyl acetate 8:2) gave 0.57g (81%) of the 4-alkyl derivative (**10d**): oil; ir (film) 1720, 1560 cm^{-1}; ^{1}H-nmr (300 MHz, $CDCl_3$) δ 1.23 (t, J = 6.9 Hz, 3 H), 1.95-2.22 (m, 2 H), 2.08 (s, 3 H), 2.43-2.64 (m, 2 H), 3.08 (d, J = 11.7 Hz, 1 H), 3.60 (d, J = 11.7 Hz, 1 H), 4.18 (q, J = 6.9 Hz, 2 H), 7.90 (s, 1 H). Anal Calcd for $C_{10}H_{15}NO_3S$: C, 52.38; H, 6.59; N, 6.11. Found: C, 52.50; H, 6.50; N, 6.25.

4-Hydroxymethyl-2-thiazoline (11). To a stirred solution of the thiazoline (**1d**) or (**1e**) (0.05 mol) in methanol (100 ml) was added portiowise $NaBH_4$ (3.7 g, 0.1 mol) in 2 h at 0 °C. After 12 h at room temperature, acetone (10 ml) was added to the reaction mixture and the solvent was removed under reduced pressure. Chromatography (silica gel, dichloromethane-methanol 96:4) gave the 4-hydroxymethyl derivative (**11**) in 75% yield from **1e** and in 67% from **1d**: bp 51-53 °C (0.02 mmHg); ir (film) 1640, 1580 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 3.12 (dd, 1 H, J = 11.0 and 9.4 Hz), 3.32 (dd, 1 H, J = 11.0 and 9.0 Hz), 3.71 (dd, 1 H, J = 11.6 and 5.4 Hz), 3.95 (dd, 1 H, J = 11.6 and 4.8 Hz), 4.45-4.85 (m, 1 H), 8.00 (d, 1 H, J = 2.6 Hz). Anal. Calcd for C_4H_7NOS: C, 41.34; H, 6.02; N, 11.95. Found: C, 41.41; H, 6.10; N, 11.88.

4-[(*tert*-Butyldimethylsilyloxy)methyl]-2-thiazoline (12). A solution of the thiazoline **11** (6.4 g, 0.054 mol), *tert* -butyldimethylsilyl chloride (9 g, 0.06 mol) and imidazole (4.08 g, 0.06 mol) in dicholoromethane (50 ml) was stirred at room temperature for 30 min. After filtration over Celite, the solvent was removed in vacuo and the residue was distilled at reduced pressure to give 9.23 g (74%) of the *tert* -butyldimethylsilyl derivative (**12**): bp 81-82° C (0.1 mmHg); ir (film) 1580, 1260 cm^{-1}; ^{1}H-nmr (300 MHz, $CDCl_3$) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.89 (s, 9 H), 3.24-3.27 (m, 2 H), 3.60 (dd, 1 H, J = 10.2 and 7.5 Hz), 3.89 (dd, 1 H, J = 10.2 and 4.2 Hz), 4.60-4.65 (m, 1 H), 7.90 (d, 1 H, J = 2.1 Hz); ^{13}C-nmr (75 MHz, $CDCl_3$), δ 5.5 (q), 18.2 (s), 25.8 (q), 33.2 (t), 64.0 (t), 78.8 (d), 158.0 (d). Anal. Calcd for $C_{10}H_{21}NOSSi$: C, 51.90; H, 9.15; N, 6.05. Found: C, 52.02; H, 9.07; N, 6.11.

Lithiation and quenching of thiazoline 12. A solution of *n* -BuLi (11 mmol) in *n* -hexane was added dropwise to a cooled (-78 °C) and stirred solution of the thiazoline **12** (10 mmol) in ether (40 ml). After 1 h stirring at -78 °C, the reaction mixture was quenched with the appropriete electrophile. Quenching of the thiazoline **12** with D_2O (0.2 ml, 10 mmol) afforded, after workup with aqueous solution of NaCl, anhydrous Na_2SO_4 and removing of the solvent under reduced pressure, the 2-deuterated derivative (**13**) in practically quantitative yield: oil; ^{1}H-nmr (300 MHz, $CDCl_3$) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.89 (s, 9 H), 3.24-3.27 (m, 2 H), 3.60 (dd, 1 H, J = 10.2 and 7.5 Hz), 3.89 (dd, 1 H, J = 10.2 and 4.2 Hz), 4.60-4.65 (m, 1 H).

Quenching of the thiazoline (**12**) with propylene oxide (0.64 g, 11 mmol) gave, after usual workup and chromatography (silica gel, petroleum ether-ethyl acetate 7:3), the thio ether (**14**) (1.38 g, 48%): oil; ir (film) 2150, 1470, 1260 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 0.01 (s, 6 H), 0.91 (s, 9 H), 1.27 (d, 3 H, J = 6.2 Hz), 2.37-2.97 (m, 5 H), 3.52-4.22 (m, 4 H).

Reaction of 2-(trimethylsilyl)-2-thiazolines (6a and 6b) with isobutyryl chloride. A solution of the proper thiazoline (1.2 mmol) and isobutyryl chloride (0.26 ml, 2.5 mmol) in benzene (30 ml) was stirred at room temperature for 24 h. The reaction mixture was washed with a saturated solution of $NaHCO_3$, dried over anhydrous Na_2SO_4 *and the solvent was removed in vacuo. Chromatography of the residue (silica gel, petroleum ether-ethyl* acetate 7:3) gave 0.094 g (50%) of the 2-acyl derivative **17** and (from **6b**) 0.108 g (30%) of the substitution product **16**.

2-Acyl derivative **17** showed the following: oil; ir (film) 1700, 1590 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 1.16 (d, J = 6.8 Hz, 6 H), 3.31 (t, J = 9.0 Hz, 2 H), 3.37-3.72 (m, 1 H), 4.52 (t, J = 9.0 Hz, 2 H); ms m/z 157 (M^+). Anal. Calcd for $C_7H_{11}NOS$: C, 53.47; H, 7.05; N, 8.91. Found: C, 53.55; H, 7.11, N, 8.80.

The condensation product **16**: mp 70-72 °C (from ether-*n*-hexane); ir ($CHCl_3$) 2960, 2920, 1645 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 1.05 (d, J = 7.0 Hz, 3 H), 1.15 (d, J = 7.0 Hz, 3 H), 1.33 (s, 3 H), 1.40 (s, 3 H), 1.55 (s, 3 H), 1.75 (s, 3 H), 2.30-3.55 (m, 5 H), 5.60 (s, 1 H); ms m/z 300 (M^+). Anal. Calcd for $C_{14}H_{24}N_2OS_2$: C, 55.96; H, 8.05; N, 9.32. Found: C, 55.84; H, 8.11; N, 9.25.

Reaction of 2-(trimethylsilyl)-2-thiazolines (6a and 6b) with isobutyraldehyde. General procedure. A mixture of the proper thiazoline (2.5 mmol) and isobutyraldehyde (0.44 ml, 5 mmol) was stirred at room temperature for 24 h to give the crude silyloxy derivatives **15**. The compound (**15a**) was chromatographed on a short column (silica gel, petroleum ether- ethyl acetate 8:2) and fully characterized: oil; ir (film) 1620 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 0.12 (s, 9 H), 0.87 (d, J = 7.0 Hz, 3 H), 0.95 (d, J = 7.0 Hz, 3 H), 1.75-2.07 (m, 1 H), 3.07-3.31 (m, 2 H), 4.12-4.37 (m, 3 H); ms m/z 231 (M^+).

The silyloxy derivatives were diluted with THF (30 ml) and then a 1 M solution of tetra-*n*-butylammonium fluoride (2.5 mmol) was added and stirring continued for 2-4 h. The solvent was removed in vacuo, the residue was diluted with ether, washed with a saturated solution of $NaHCO_3$ and dried over anhydrous Na_2SO_4. After removing of the solvent, the residue was chromatographed (silica gel, petroleum ether-ethyl acetate 1:1) to give the corresponding alcohols **7a** (0.14 g, 35%) and **7b** (0.23 g, 50%) respectively.

The alcohol (**7b**) showed the following: mp *77-79 °C (from ethyl acetate-petroleum ether); ir ($CHCl_3$) 1655 cm^{-1}*; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 0.95 (d, J = 11.0 Hz, 3 H), 1.02 (d, J = 11.0 Hz, 3 H), 1.37 (s, 3 H), 1.42 (s, 3 H), 1.75-2.07 (m, 1 H), 3.17 (s, 2 H), 3.32 (br s, 1 H), 4.22 (d, J = 4.0 Hz, 1 H). Anal. Calcd for $C_9H_{17}NOS$: C, 57.70; H, 9.15; N, 7.48. Found: C, 57.81; H, 9.10; N, 7.42.

Reaction of 2-(trimethylsilyl)-2-thiazolines (6a) with 1,2,3,4-di-*O*-isopropylidene-α-*D*-*galacto*-hexodialdo-1,5-pyranose. A solution of the thiazoline (0.35 g, 2.1 mmol) and the chiral aldehyde (0.55 *g, 2.1 mmol) in dry benzene (50 ml)* was stirred at room temperature for 48 h. The solvent was removed in vacuo and the residue was diluted with THF (30 ml) and then a 1 M solution of tetra-*n*-butylammonium fluoride (2.1 ml, 2.1

mmol) was added and stirring continued for 2-4 h. The solvent was removed in vacuo, the residue was dissolved in ether, washed with a saturated solution of $NaHCO_3$ and dried over anhydrous Na_2SO_4. After removing of the solvent, the residue was chromatographed (silica gel, petroleum ether-ethyl acetate 1:1) to give 0.34 g (50%) of the alcohol (**19**) (ds ≥ 95% by nmr spectrum): syrup oil; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 1.32 (s, 3 H), 1.37 (s, 3 H), 1.49 (s, 3 H), 1.52 (s, 3 H), 3.35 (t, J = 8.4 Hz, 2 H), 3.77-4.73 (m, 8 H), 5.53 (d, J = 5.0 Hz, 1 H); ms m/z 345 (M^+). Anal. Calcd for $C_{15}H_{25}NO_6S$: C, 52.16; H, 6.71; N; 4.05. Found: C, 52.25; H, 6.66; N, 4.00.

Reaction of 4,4-dimethyl-2-(trimethylsilyl)-2-thiazolines (6b) with 1,2-*O*-isopropylidene-3-*O*-benzyl-α-*D*-*xylo*-pentodialdofuranose. A solution of the thiazoline (0.37 g, 2 mmol) and the chiral aldehyde (0.55 g, 2 mmol) in dry benzene (50 ml) was stirred at room temperature for 5 days. Workup as above for **6a** and chromatography gave 0.23 g (30%) of the alcohol (**18**) (ds = 85% by nmr spectrum): syrup oil; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 1.30 (s, 6 H), 1.32 (s, 3 H), 1.35 (s, 3 H), 3.07 (s, 2 H), 3.93-4.90 (m, 7 H), 6.00 (d, J = 4.0 Hz, 1 H), 7.32 (s, 5 H); ms m/z 393 (M^+). Anal. Calcd for $C_{20}H_{27}NO_5S$: C, 61.04; H, 6.92; N, 3.56. Found: C, 60.95; H, 6.98; N, 3.51.

Lithiation of 4-[(*tert*-butyldimethylsilyloxy)methyl]-2-thiazoline (12) and reaction with aldehydes. General procedure. A solution of *n*-BuLi (1.2 mmol) in *n*-hexane was added dropwise to a cooled (-78 °C) and stirred solution of the thiazoline **12** (0.23 g, 1 mmol) in ether (30 ml). After 1 h stirring at -78 °C, the reaction mixture was quenched with the selected aldehyde (1.2 mmol). Workup with NaCl as above for **1a** and chromatography (silica gel, petroleum ether-ether 7:3) gave with benzaldehyde 0.15 g (45%) of the alcohols **20a** and **20a'** in 3:1 diastereomeric ratio and with isobutyraldehyde 0.03 g (10%) of the diastereomeric pure alcohol **20b**.
Compound **20a** (the major diastereoisomer) : ^{1}H-nmr (300 MHz, $CDCl_3$) δ 0.06 (s, 3 H), 0.07 (s, 3 H), 0.88 (s, 9 H), 1.75 (br s, 1 H), 3.33-3.40 (m, 2 H), 3.63 (dd, 1 H, J = 7.3 and 10.8 Hz), 3.85 (dd, 1 H, J = 4.3 and 10.8 Hz), 4.63-4.67 (m, 1 H), 5.37 (s, 1 H), 7.27-7.44 (m, 5 H); compound **20a'** (the minor diastereoisomer): ^{1}H-nmr (300 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.89 (s, 9 H), 1.29 (br s, 1 H), 3.35 (d, 2 H, J = 8.1 Hz), 3.69 (dd, 1 H, J = 7.1 and 9.7 Hz), 3.89 (dd, 1 H, J = 4.1 and 9.7 Hz), 4.60-4.64 (m, 1 H), 5. 38 (s, 1 H), 7.26-7.44 (m, 5 H). Anal. Calcd for $C_{17}H_{27}NO_2SSi$: C, 60.49; H, 8.06; N, 4.15. Found: C, 60.38; H, 8.00; N, 4.09.
Compound **20b**: oil; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.91 (m, 12 H), 1.05 (d, 3 H, J = 9.7 Hz), 1.96 (m, 1 H), 3.38-3.42 (m, 2 H), 3.65 (dd, 1 H, J = 7.5 and 11.2 Hz), 3.92 (dd, 1 H, J = 4.5 and 11.2 Hz), 4.25 (d, 1 H, J = 3.7 Hz), 4.57-4.63 (m, 1 H). Anal. Calcd for $C_{14}H_{29}NO_2SSi$: C, 55.40; H, 9.63; N, 4.61. Found: C, 55.51; H, 9.55; N, 4.45.

Formylation of thiazoline 12 and reduction to 2-hydroxymethyl derivative 21. A solution of *n*-BuLi (2.3 mmol) in *n*-hexane was added dropwise to a cooled (-78 °C) and stirred solution of the thiazoline **12** (0.5 g, 2.1 mmol) in ether (30 ml). After 1 h stirring at -78 °C, the reaction mixture was quenched with *N*-formylmorpholine (0.37 g, 3.2 mmol) in the same solvent (10 ml). Attempt to separate the 2-formyl derivative with usual workup produced a rapid decomposition of the compound. So to the reaction mixture was added methanol (10 ml) and sodium borohydride (0.08 g, 2.1 mmol). After 30 min, acetone (2 ml) was added to the reaction mixture and the solvent was removed under reduced pressure. The residue was chromatographed (silica gel, petroleum ether-ether 7:3) to give

0.27 g (50%) of the 2-hydroxymethyl-2-thiazoline **21**: oil; ^{1}H-nmr (300 MHz, $CDCl_3/D_2O$) δ 0.07 (s, 3 H), 0.08 (s, 3 H), 0.89 (s, 9 H), 3.45 (dd, 2 H, J = 6.0 and 8.8 Hz), 3.65 (dd, 1 H, J = 7.5 and 10.2 Hz), 3.87 (dd, 1 H, J = 4.5 and 10.2 Hz), 4.38 (d, 2 H, J = 1.9 Hz), 4.56-4.68 (m, 1 H); ^{13}C-nmr (75 MHz, $CDCl_3$) δ -5.6 (q), 18.2 (s), 25.9 (q), 39.6 (t), 49.4 (d), 62.4 (t), 62.8 (t), 173.5 (s). Anal. Calcd for $C_{11}H_{23}NO_2SSi$: C, 50.53; H, 8.87; N, 5.36. Found: C, 50.62; H, 8.79; N, 5.40.

Reaction of 2-formylthiazoline with phosphonium salt. General procedure. Formylation was carried out as above and the 2-formyl derivative was treated with the appropriate phosphonium salt (1 equiv.) at 0 °C. After stirring overnight at room temperature, a saturated solution of NaCl was added. The organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was removed in vacuo and chromatography of the residue (silica gel, petroleum ether-ethyl acetate 8:2) gave the E-alkenes **22a** (68%), **22b** (58%) and **22c** (16%).

The E-alkene **22a** showed the following: oil; ir (film) 1635, 1585 cm^{-1}; ^{1}H-nmr (300 MHz, $CDCl_3$) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.90 (s, 9 H), 3.37-3.42 (m, 2 H), 3.67 (dd, 1 H, J = 7.8 and 10.0 Hz), 3.95 (dd, 1 H, J = 4.3 and 10.0 Hz), 4.72-4.76 (m, 1 H), 7.24 (d, 1 H, J = 16.1 Hz), 7.31 (d, 1 H, J = 16.1 Hz), 7.35 (d, 1 H, J= 3.2 Hz), 7.87 (d, 1 H, J = 3.2 Hz);. ^{13}C-nmr (75 MHz, $CDCl_3$) δ -5.8 (q), 17.91 (s), 25.54 (q), 34.73 (t), 63.70 (t), 79.17 (d), 120.51 (d), 127.81 (d), 133.05 (d), 144.72 (d), 165.12 (s), 167.51 (s); ms m/z M^+ absent, 283, 176, 147, 88. Anal. Calcd for $C_{15}H_{24}N_2OS_2Si$: C, 52.90; H, 7.10; N, 8.22. Found: C, 52.81; H, 7.16; N, 8.17.

The E-alkene **22b**: oil; ir (film) 1730, 1650, 1585 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.88 (s, 9 H), 1.32 (t, 3 H, J = 7.2 Hz), 3.38 (d, 2 H, J = 8.6 Hz), 3.67 (dd, 1 H, J = 7.6 and 10.6 Hz), 3.92 (dd, 1 H, J = 4.4 and 10.6 Hz), 4.25 (q, 2 H, J= 7.2 Hz), 4.55-4.82 (m, 1 H), 6.35 (d, 1 H, J = 16.2 Hz), 7.37 (d, 1 H, J = 16.2 Hz); ^{13}C-nmr (75 MHz, $CDCl_3$) δ -5.51 (q), 14.09 (q), 18.19 (s), 25.84 (q), 34.91 (t), 61.29 (t), 63.86 (t), 78.61 (d), 130.51 (d), 137.78 (d), 166.09 (s), 167.32 (s); ms m/z M^+ absent, 272, 147. Anal. Calcd for $C_{15}H_{27}NO_3SSi$: C, 54.82; H, 8.26; N, 4.25. Found: C, 54.77; H, 8.20; N, 4.29.

The E-alkene **22c**: oil; ir (film) 1635, 1590 cm^{-1}; ^{1}H-nmr (80 MHz, $CDCl_3$) δ 0.65 (s, 3 H), 0.75 (s, 3 H), 0.90 (s, 9 H), 3.31 (dd, 2 H, J = 8.0 and 11.0 Hz), 3.57-3.77 (m, 1 H), 3.95 (dd, 1 H, J = 4.0 and 10.0 Hz), 4.61-4.82 (m, 1 H), 6.92 (d, 1 H, J = 13 Hz), 7.12 (d, 1 H, J = 13 Hz), 7.22-7.55 (m, 5 H); ms m/z M^+ absent, 276, 100. Anal. Calcd for $C_{18}H_{27}NOSSi$: C, 64.81; H, 8.16; N, 4.20. Found: 64.70; H, 8.23; N, 4.15.

REFERENCES

1 A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, J. Org. Chem., **1988**, 53, 1748.

2 A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, J. Org. Chem., **1987**, 52, 3417.

3 A. Dondoni, G. Fantin, M. Fogagnolo, A. Mastellari, A. Medici, E. Negrini, and P. Pedrini, Gazz. Chim. Ital., **1987**, 118, 211.

4 A. Dondoni, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, Synthesis, **1987**, 693.

5 O. Bortolini, G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, Heterocycles, **1990**, 31, 1213.

6 Other reducing agents and solvents were tested ($NaBH_4$ in MeOH, $NaBH_4$ in THF/EtOH buffer at pH = 7, Bu_4NBH_4 in CH_2Cl_2, $NaBH_4(SiO_2)_x$, $LiBH_4$ in THF) with worse results.

7 The reaction was carried out with NaH/MeI, BuLi/MeI at -78°C in ether and CH_2N_2/aluminum oxide.

8 A. Dondoni , G. Fantin, M. Fogagnolo, A. Medici, and P. Pedrini, J. Org. Chem., **1989**, 54, 693.

9 M. Cherest, H. Felkin, and N. Prudent, Tetrahedron Lett., **1968**, 2199; N. T. Anh, Top Curr. Chem., **1980**, 88, 145.

10 The major product, on standing in $CDCl_3$ (24 h), afforded the corresponding ketone; the minor product,in the same conditions, converted to the major and then gave the ketone. This behaviour has been detected with other secondary alcohols subtituted with heterocyclic and/or aromatic ring (ref. 1).

11 H. Wenker, J. Am. Chem. Soc., **1935**, 57, 1079.

12 A. I. Meyers, J. Org. Chem., **1960**, 25, 1147

13 J. Laduranty, F. Barbott, and L. Miginiac, J. Organomet. Chem., **1987**, 335, 283.

14 M. R. Bells, J. A. Carlson, and R. Oesterlin, J. Org. Chem., **1972**, 37, 2733.

15 Optically pure Δ^2-thiazoline (**1b**) or (**1c**) can be obtained from L-cysteine methyl ester or ethyl ester following the procedure described by : Y. Nagao, T. Kumagai, S. Takao, T. Abe, M. Ochiai, Y. Inoue, T. Taga, and E. Fujita J. Org. Chem., **1986**, 51, 4737.

16 A. I. Meyers, G. Knaus, K. Kamata, and M. E. Ford, J. Am. Chem. Soc., **1976**, 98, 567.

17 L-Cysteine was used because of its cheapness but during the reaction we have complete racemization.

18 G. B. Howarth, D. G. Lance, W. A. Szarek, and J. K. N. Jones, Can. J. Chem. , **1969**, 47, 75.

19 M. L. Wolfrom and S. Hanessian, J. Org. Chem., **1962**, 27, 1800.

Received, 7th July, 1992