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A CONCISE THIAZOLE MEDIATED SYNTHESIS OF L-(-)-RHODINOSE FROM (S)-ETHYL LACTATE. THE THIAZOLE ROUTE TO DEOXYSUGARS [1]

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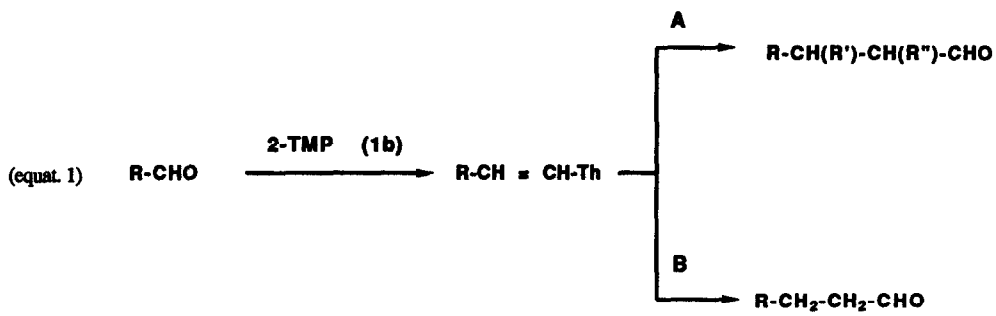
Summary 2-Lithiothiazole (2-LTT) (**1a**) and 2-thiazolylmethylenetriphenylphosphorane (2-TMP) (**1b**) are employed as aldehyde equivalents in a new concise synthesis of 4-*O*-tert-butyldimethylsilyl L-(-)-rhodinose (**2b**) from (*S*)-ethyl lactate The key intermediates in the synthesis are two differentially protected hydroxyl aldehydes, i e the 4-deoxy-L-threose derivative **3b** and the (*S*,*S*)-4,5-dihydroxyhexanal derivative **4b** which are obtained in high yield starting from *O*-benzyloxymethyl (*S*)-ethyl lactate (**5**) The selective C_5 hydroxyl deprotection in **4b** leads to the TBS-protected rhodinose **2b** in the pyranose form A complete ^1H and ^{13}C NMR analysis of **2b** is provided.

In previous papers of this series,[2] we have outlined new methods for the construction of chiral polyhydroxylated aldehydes, i e carbohydrate-like materials, by using two substituted thiazoles at C_2 as effective synthetic equivalents to aldehyde synthons This concept is now extended to another thiazole derivative In fact, the Wittig olefination of an aldehyde with 2-thiazolylmethylenetriphenylphosphorane[3] (2-TMP) (**1b**), followed by an appropriate elaboration of the resulting vinylthiazole, i e the sequential functionalization of the ethylenic bond and the formyl deblocking from the thiazole ring,[4] transforms the original aldehyde into a functionalized two-carbon higher homologue (eq 1, Route A) Alternatively, the one-pot formyl release from the thiazole ring and the concomitant reduction of the ethylenic bond, leads to an unbranched saturated homologue (route B)[3] This overreduction has been conveniently exploited for the side chain-elongation of dialdoses into 2,3-dideoxy higher homologues[5] We would like to report here the application of this strategy toward a target deoxysugar, i e L-(-)-rhodinose (**2**), the well known glycidic subunit of bioactive compounds such as the antibiotic streptolydigin[6a] and various oligosaccharides present in the rhodomycin family of anthracycline antibiotics[6b]

1

a, R = Li
b, R = $^{-}$CH-P^{+}Ph$_3$

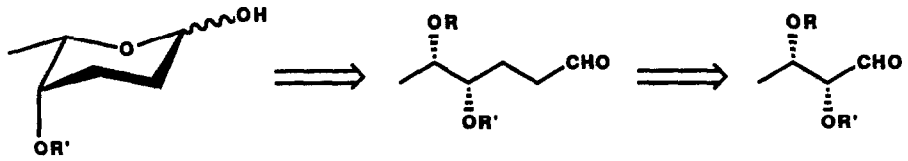


Results

L-(-)-Rhodinose (**2a**) and its derivatives[7] have been prepared previously by a number of synthetic routes starting either from sugar precursors[8] or from non-congener materials.[9] New methods for the construction of this relatively simple molecule are still of considerable interest. In order to overcome some limitations of the literature procedures and provide a full characterization of the target products, Schlessinger and Graves have described recently[10] a five-step route to 4-*O*-t-butyldimethylsilyl L-(-)-rhodinose (**2b**) and to the parent compound[7] **2a** from (*S*)-ethyl lactate via the differentially hydroxyl protected 4,5-dihydroxyhexanal **4a**. This prompted us to report here our thiazole-mediated strategy to **2b** which involves the key intermediate **4b** obtained by a different route than **4a**. A complete NMR analysis provides a full characterization of **2b** and clarifies some discrepancies in earlier NMR spectra.[10]

A simple disconnection in the aldehyde **4** reveals that this compound should be accessible from a protected 4-deoxy-L-threose (**3**) via reaction with 2-TMP (**1b**) (eq. 1, route B). In view of the extensive use of the aldehyde **3** as a key intermediate to L-deoxy- and L-aminosugars,[11] various protected forms of this compound have been prepared from natural tartaric acid or from D-threonine,[12] and very recently from (*S*)-ethyl lactate[13] and lactaldehyde.[14] However, for a variety of reasons,[15] none of the reported methods, including the one from our laboratory,[14] appealed to us as a means of preparing a suitable differentially protected derivative of **3a**.

We decided to prepare 2-*O*-TBS-protected 3-*O*-benzyloxymethyl-4-deoxy-L-threose (**3b**) starting from the easily available *O*-benzyloxymethyl (*S*)-ethyl lactate[16] (**5**) (Scheme I) via our thiazole-mediated acylation-reduction sequence.[17] Reasons for chosing this route were the high levels of diastereoselectivity observed in the reduction of acylthiazoles bearing an α-chiral center[17] and the well proven use of the thiazole ring as an effective, and in some cases superior formyl equivalent.[2]



2 4 3

a, R' = H
b, R' = $SiMe_2Bu$-t

a, R = CH_2Ph
R' = $SiMe_2Bu$-t
b, R = CH_2OCH_2Ph
R' = $SiMe_2Bu$-t

a, R = R' = H
b, R = CH_2OCH_2Ph
R' = $SiMe_2Bu$-t

The benzyloxymethyl (BEN) group was selected for protection of one hydroxyl since it is stable enough and can be easily removed under very mild conditions [18] The reaction of **5** with 2-lithiothiazole (2-LTT) (**1a**), generated in situ from 2-bromothiazole (**6**) and n-butyl lithium, afforded the BEN-protected α-hydroxyacylthiazole **7** (90 %) which was reduced with L-Selectride to give the expected[17] *syn*-diol **8a** (ds = 93%) according to the non-chelate Felkin-Anh model for diastereoselection [19] The stereochemistry of **8a** was confirmed by comparison of the NMR spectrum and physical properties of the *O*-benzyl derivative **8c** with those of the same product obtained from other routes [14,20] After reaction of crude **8a** with t-butyldimethylsilyl chloride, the *O*-TBS derivative *syn*-(**8b**) was purified from the very small amount of the *anti*-isomer[21] (**8b'**) by flash chromatography . Then, compound **8b** was converted into the target aldehyde **3b** (70 %) by one-pot formyl release from the thiazole ring[2,5] via sequential *N*-methylation, reduction, and hydrolysis Owing to the high yield in each step of the sequence and the excellent degree of diastereoselectivity in the reduction of the ketone **7**, this thiazole-mediated route from **5** to **3b** appears to be quite convenient This result confirms the effectiveness of the acylation-reduction strategy for the installation of *syn*-1,2-diol fragments adjacent to the formyl group [17]

As anticipated above, we commenced the two-carbon chain elongation of the aldehyde **3b** by Wittig olefination using 2-TMP (**1b**), generated in situ from the appropriate phosphonium chloride **9** and potassium t-butoxide (Scheme II) The resulting vinylthiazole **10** (60 %), obtained essentially as the *E*-isomer, was subjected to the usual one-pot formyl deblocking sequence, affording the protected (*S,S*)-4,5-dihydroxyhexanal **4b** in 55 % isolated yield As expected from earlier work,[3] the 2-alkyl *N*-methylthiazolidine **11** as a fully saturated intermediate from **10** to **4b** was demonstrated [22] The selective hydrogenolytic deprotection of the C_5 hydroxyl in **4b** occurred under very mild conditions, i e in methanol solution at room temperature with a stream of hydrogen in the presence of Palladium (10 % on charcoal), to give 4-*O*-TBS L-(-)-rhodinose (**2b**) in 89 % isolated yield. Compound **2b**, which exists as a mixture of α and β anomers in the pyranose form,[7] presented physical data, namely $[\alpha]_D$ = -13 4° (c 1 85, CH_2Cl_2) and mp = 69-70° C, in agreement with those of the literature,[10] and showed consistent ^1H and ^{13}C NMR spectra The spectra of **2b**, however do not correspond completely with those reported for the same compound by Schlessinger and Graves [10] Some inconsistent multiplicities of ^1H signals (4 11, q collapsing to d on addition of D_2O, 1 22, t, 1 14, t) and an

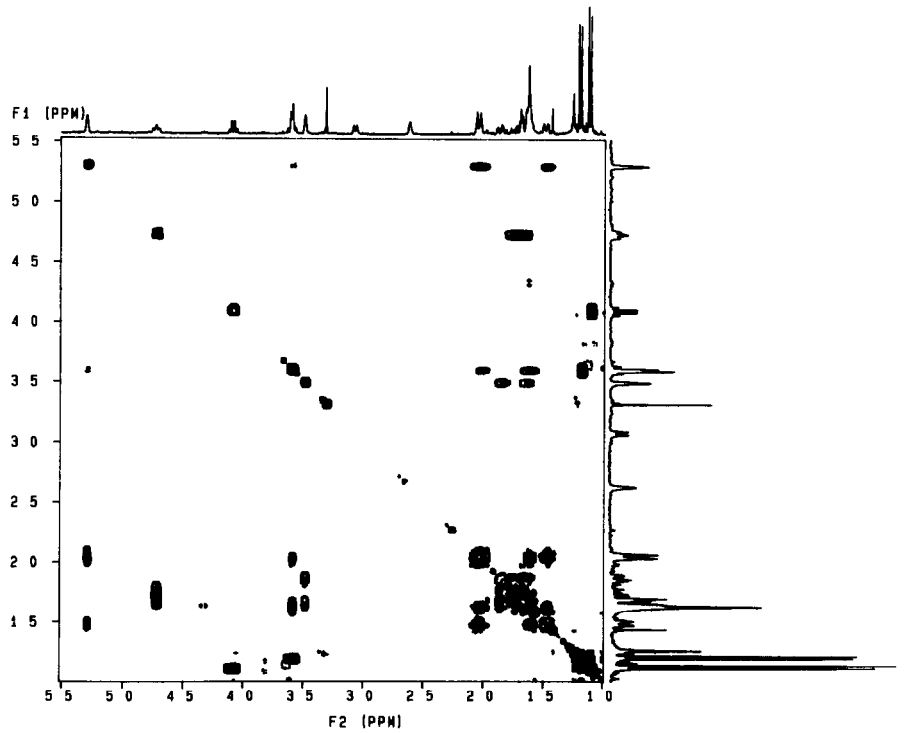


Figure 1 ^{1}H-^{1}H homonuclear chemical shift correlation spectrum of 4-*O*-TBS L-(-)- Rhodinose (**2b**)

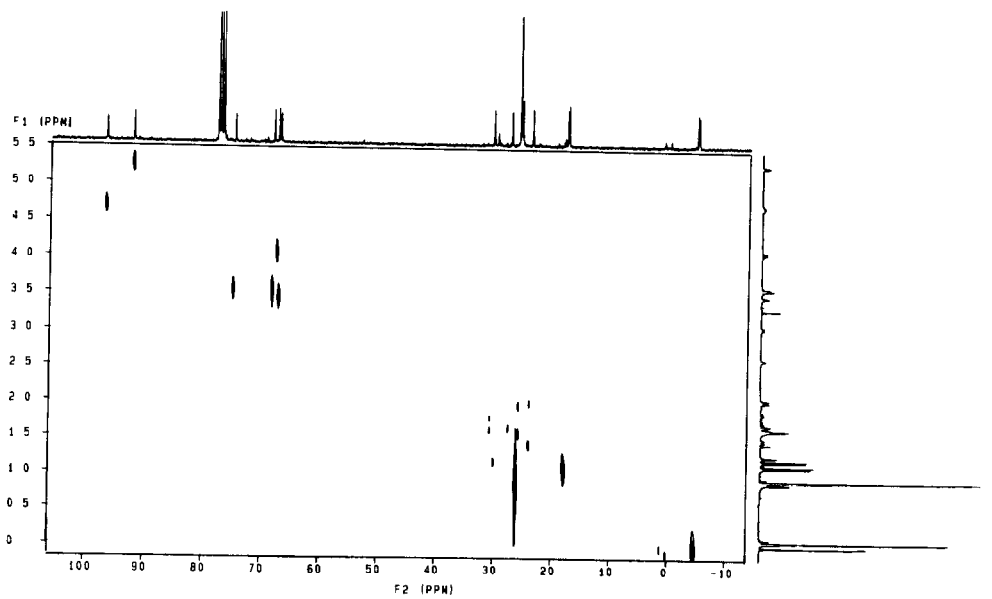
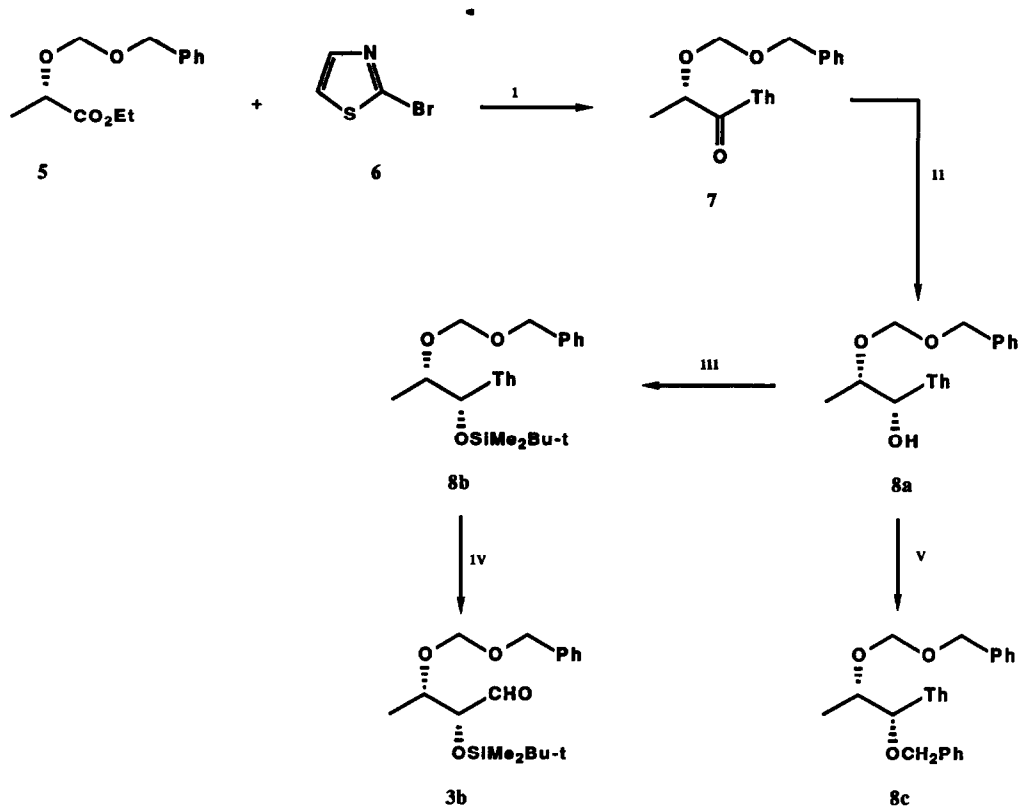


Figure 2. ^{1}H-^{13}C heteronuclear chemical shift correlation spectrum of 4-*O*-TBS L-(-)-Rhodinose (**2b**)

SCHEME I

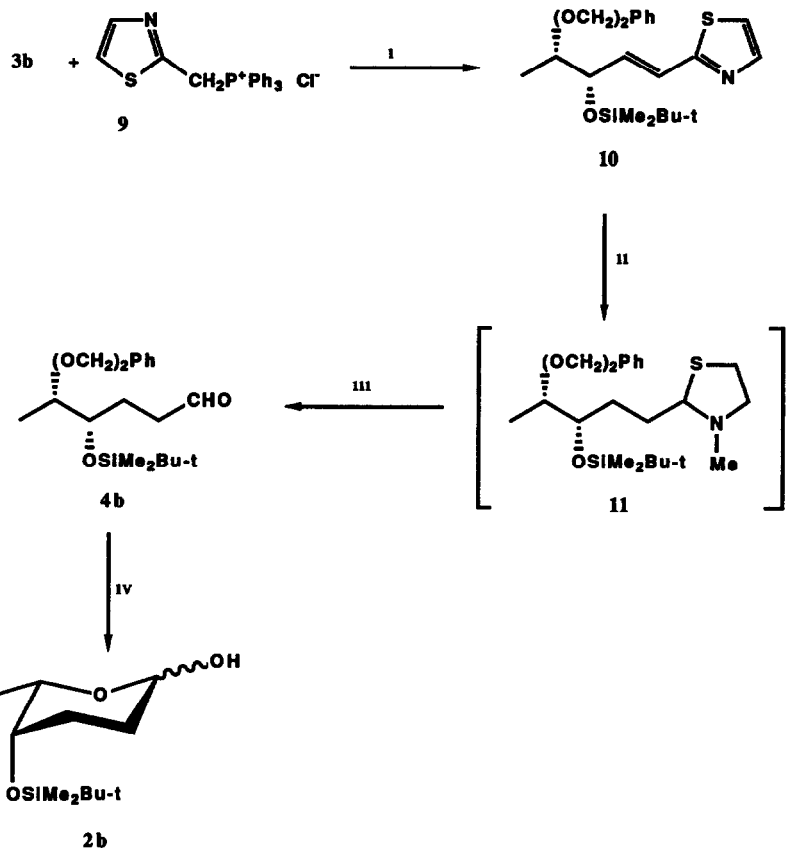


Reagents i) n-BuLi (Et_2O, -78 °C) ii) LiB(Bu-s)$_3$H (THF, -80 °C) iii) t-BuMe$_2$SiCl, Imidazole (DMF, rt). iv) a, MeI (MeCN, reflux); b, $NaBH_4$ (MeOH, -10 °C), c, $HgCl_2$ (MeCN/H_2O, rt) v) NaH, $PhCH_2Br$ (THF, reflux)

excessive number of ^{13}C signals are observed In order to clarify these discrepancies in NMR spectra, a full assignement of signals in the spectra of **2b** has been made by using two-dimensional homo- and hetero-correlation spectroscopy [23] The ^1H-^1H COSY (Fig 1) and ^1H-^{13}C HETCOR (Fig 2) clarified the chemical shifts and the coupling patterns of the overlapped ^1H signals and afforded the full correlation of the ^1H signals with the ^{13}C signals These data demonstrate the identity of 4-*O*-TBS (L)-(-)-rhodinose (**2b**) prepared by the Thiazole Route quite convincingly and indicate that the NMR spectra reported by Schlessinger and Graves[10] have to be corrected

In conclusion, a new concise thiazole-mediated route to rhodinose in its exclusive pyranose form has been described This route, for its simplicity and high yields in each step, complements other synthetic methods to this deoxysugar and indicates a new strategy toward other important isomers, such as boivinose, digitoxose etc [6]

SCHEME II



Reagents i) BuOK-t (THF, rt) ii) a, MeI (MeCN, reflux); b, $NaBH_4$ (MeOH, -10 °C) iii), $HgCl_2$ (MeCN/H_2O, rt). iv) H_2 (Pd, 10% on charcoal, MeOH)

Experimental

General Procedures and Materials. All melting and boiling points are uncorrected All experiments were carried out under nitrogen and with freshly distilled and dried solvents The spectrometers for NMR and IR measurements and the apparatus for elemental analyses were as described [2,3] 2-Bromothiazole (**6**) was commercially available (Aldrich or Fluka) and *O*-benzyloxymethyl (*S*)-ethyl lactate (**5**) was obtained according to the literature procedure [16] 2-Thiazolylmethylenetriphenylphosphonium chloride (**9**) was prepared as described [3]

2-[(S)-2-(Benzyloxymethoxy)propanoyl]thiazole (7). A solution of 2-bromothiazole (6) (3 80 g , 23.1 mmol) in diethyl ether (30 mL) was added over 3O min to a stirred solution of n-BuLi (23.1 mmol) in the same solvent (5O mL) at -78°C. After stirring the reaction mixture for 3O min , a solution of *O*-benzyloxymethyl (*S*)-ethyl lactate (5) (5.O g, 21 mmol) in diethyl ether (3O mL) was added dropwise in 5 min After 1O min. at -78°C, the reaction mixture was allowed to warm to room temperature and washed with saturated $NaHCO_3$ The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. Cromathography of the residue (silica gel, 9 1 petroleum ether diethyl ether) gave the α-alkoxy acylthiazole (7) (5.24 g, 9O %) · oil, IR (film) 31OO, 17OO, 148O cm^{-1}, ^1H NMR (8O MHz, $CDCl_3$) δ 1.58 (d, 3 H, *J* = 7.O Hz), 4 6O (s, 2 H), 4 86 (s, 2 H), 5 42 (q, 1 H, *J* = 7 O Hz), 7.25 (s, 5 H), 7.65 (d, 1 H, *J* = 3 2 Hz), 7 97 (d, 1 H, *J* = 3 2 Hz)

Anal Calcd for $C_{14}H_{15}O_3NS$ C, 60 64; H, 5 45, N, 5 O5 Found C, 6O 58, H, 5 41, N, 5 O8

Reduction of α-Alkoxy Acylthiazole (7). The ketone 7 (2 5 g, 9 mmol) was dissolved in tetrahydrofuran (5O mL) and the solution cooled to -78°C L-Selectride (1M in THF, 18 mL) was added and stirring was continued for 3O min at -78°C The mixture was carefully quenched with a solution of 1O% KOH (15 mL) and 3O % H_2O_2 (1O mL) and then allowed to warm to room temperature After 4 h stirring, the reaction mixture was diluted with brine (2O mL) and extracted with diethyl ether (3 x 5O mL) The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure The residue was cromatographed through a short column (silica gel, 7 3 petroleum ether : ethyl acetate) to give 2 38 g (95 %) of an oil which resulted to be a mixture of **(1R)-2-*O*-benzyloxymethyl-3-Deoxy-1-(2-thiazolyl)-L-glycitol (8a)** and its epimer **(8a')** in 93 7 ratio The major isomer (**8a**) showed the following ^1H NMR (8O MHz, C_6D_6, D_2O) δ 1 16 (d, 3 H, *J* = 6 4 Hz), 4 2O (m, 1 H), 4 3O (s, 2 H), 4 5O (s, 2 H), 4.87 (d, 1 H, *J* = 5.O Hz), 6 62 (d, 1 H, *J* = 3 2Hz), 7 15 (m, 5 H) , 7 5O (d, 1 H, *J* = 3 2 Hz) (**8a'**) showed δ 5.O9 (1 H, d, *J* = 3.6 Hz)

Anal Calcd for $C_{14}H_{17}O_3NS$ C, 6O 2O, H, 16 14, N, 5 O2 Found C, 6O 25, H, 6.17, N, 5 O7

(1R)-1-O-tert-Butyldimethylsilyl-2-O-Benzyloxymethyl-3-Deoxy-1-(2-Thiazolyl)-L-glycitol (8b). The mixture of **8a** and its epimer **8a'** (2 3 g , 8 2O mmol) was dissolved in DMF (5 mL) and then treated with imidazole (1 4 g, 2O 5 mmol) and tert-butyldimethylsilyl chloride (1 48 g, 9 84 mmol) at room temperature After 8 h, the solvent was removed in vacuo, the residue treated with brine (5O mL) and extracted with petroleum ether (3 x 5O mL) The organic layer was dried (Na_2SO_4) and the solvent removed under vacuum Flash chromatography of the residue (silica gel, 8 1 1 petroleum ether diethyl ether benzene) afforded 2.8 g (86 %) of pure **8b** as a colorless oil ^1H NMR (8O MHz, C_6D_6) δ -O O2 (s, 3 H), O O6 (s, 3 H), O 96 (s, 9 H), 1 22 (d, 3 H, *J* = 6 2 Hz), 4 1O (m, 1 H), 4 5O (s, 2 H), 4 75 (s, 2 H), 5 17 (d, 1 H, *J* = 5 2 Hz), 6.65 (d, 1 H, *J* = 3 2 Hz), 7 15 (m, 5 H), 7 52 (d, 1 H, *J* = 3 2 Hz)

Anal Calcd for $C_{20}H_{31}O_3NSSi$ C, 61 O3, H, 7 94, N, 3 56 Found C, 61 O8, H, 7 98, N, 3 5O

2-O-tert-Butyldimethylsilyl-3-O-Benzyloxymethyl-4-Deoxy-L-Threose (3b). A solution of **8b** (2 8 g, 7 12 mmol) and methyl iodide (1O g, 71.2 mmol) in acetonitrile (6O mL) was refluxed for 8 h The solvent was removed under vacuum and the crude *N*-methylthiazolium salt was dissolved in methanol (5OmL) After cooling the solution at -1O° C, sodium borohydride (O 54 g, 14 2 mmol) was added portionwise and the mixture stirred for 2O min The mixture was quenched with

acetone (2 mL), the solvent was partially evaporated under vacuum and, after addition of brine (20 mL), the residue was extracted with diethyl ether The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo The resulting crude thiazolidine was dissolved in acetonitrile (5mL) and added to a stirred solution of $HgCl_2$ (2 0 g, 7 8 mmol) in a 4 1 acetonitrile-water mixture (30 mL) After 15 min, the solvent was partially evaporated under vacuum and, after addition of diethyl ether (20 mL), the mixture was filtered through celite The organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed in vacuo. The aldehyde **3b** (1 68g ,70 %), taken up with pentane (30 mL), showed the following oil, IR (film), 1740 cm^{-1}, ^1H NMR (80 MHz, $CDCl_3$) δ 0 09 (s, 3 H), 0 12 (s, 3 H), 0 93 (s, 9 H), 1 28 (d, 3 H, J = 6 2 Hz), 4 06 (m, 2 H), 4 60 (s, 2 H), 4 78 (s, 2 H), 7 31 (s, 5 H), 9 68 (d, 1 H, J = 1 1 Hz) This compound was sufficiently pure for further use

(1R)-1-O-Benzyl-2-O-Benzyloxymethyl-3-Deoxy-1-(2-Thiazolyl)-L-glycitol (8c). The mixture of **8a** and its epimer **8a'** (0 23 g, 0 82 mmol) in dry THF (10 mL) was treated portionwise with sodium hydride (50 % dispersion in mineral oil (0 043 g, 0 90 mmol) at room temperature The reaction mixture was gently refluxed for 10 min and then benzyl bromide (0 15 g, 0 90 mmol) and a catalytic amount of tetra-n-butylammonium iodide were added sequentially After 24 h at room temperature, the solvent was partially evaporated at reduced pressure, saturated aqueous solution (5 mL) of $NaHCO_3$ was added and the mixture was extracted with dichloromethane The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure The residue was chromatographed (silica gel, 7 3, petroleum ether diethyl ether) to give 0 24 g (82 %) of the *O*-benzyl derivative **8c**[20] oil, ^1H NMR (80 MHz, C_6D_6) δ 1 16 (d, 3 H, J = 6 4 Hz), 4 1-4 95 (m, 8 H), 6 67 (d, 1 H, J = 3 2 Hz), 7 12 (m, 10 H), 7 53 (d, 1 H, J = 3 2 Hz)

Anal Calcd for $C_{21}H_{23}O_3NS$ C, 68 28, H, 6 28, N, 3 79 Found C, 68 31, H, 6 30, N, 3 75

(3S,4S)-4-O-Benzyloxymethyl-3-O-tert-Butyldimethylsilyl-1-(2-thiazolyl)-pent-1-ene E-(10). To a stirred suspension of 2-thiazolylmethylenetriphenylphosphonium chloride (**9**) (1 68 g, 4.26 mmol) in anhydrous THF (30 mL) was added potassium tert-butoxide (0 48 g, 4 26 mmol) After 30 min at room temperature, the resulting yellow mixture was treated with a solution of the aldehyde **3b** (1.2 g, 3 55 mmol) in THF (15 mL) and stirring was continued for 48 h The reaction mixture was filtered through celite, the solvent removed under vacuum and the residue chromatographed (silica gel, 9 1, petroleum ether diethyl ether) to give 0 89 g (60 %) of the *E*-alkene (**10**) oil, ^1H NMR (300 MHz, $CDCl_3$) δ 0 04 (s, 3 H), 0 05 (s, 3 H), 0 93 (s, 9 H), 1 15 (d, 3 H, J = 6 4 Hz), 3 85 (m, 1 H), 4 44 (m, 1 H), 4 65 (s, 2 H), 4 86 (s, 2 H), 6 73 (dd, 1 H, J = 16 Hz, J = 4 5 Hz), 6 93 (dd, 1 H, J = 16 Hz, J = 0 6 Hz), 7 23 (d, 1 H, J = 3 3 Hz), 7 35 (m, 5 H), 7 77 (d, 1 H, J = 3 3 Hz)

Anal Calcd for $C_{22}H_{33}NO_3SSi$ C, 62 98, H, 7 93, N, 3 34 Found C, 62 90, H, 8 01, N, 3 29

2,3,6-Trideoxy-4-O-tert-Butyldimethylsilyl-5-O-Benzyloxymethyl-L-Threo-Hexose (4b). The 2-ethenylthiazole (**10**) (0 7 g, 1 67 mmol) was treated sequentially with methyl iodide (2 37 g, 16 7 mmol), sodium borohydride (0 13 g, 3 34 mmol), and mercury chloride (0 45 g, 1 84 mmol) as described for the unmasking of **3b** from **8b** The final material was chromatographed through a short column (silica gel, 9 1, petroleum ether diethyl ether) to give 0 34 g (55 %) of the pure aldehyde **4b** oil, $[\alpha]_D$ = -19 1 (c 1 92, CH_2Cl_2), IR (film), 1730 cm^{-1}, ^1H NMR (80 MHz,

$CDCl_3$) δ 0.06 (s, 6 H), 0.90 (s, 9 H), 1.15 (d, 3 H, J = 6.0 Hz), 1.50-2.65 (m, 4 H), 3.70 (m, 2 H), 4.60 (s, 2 H), 4.73 (s, 2 H), 7.28 (s, 5 H), 9.72 (br t, 1 H)

Anal Calcd for $C_{20}H_{34}O_4Si$ C, 65.53, H, 9.35. Found : C, 65.56, H, 9.39.

2,3,6-Trideoxy-4-O-tert-Butyldimethylsilyl-L-Threo-Hexopyranose (2b). To a stirred solution of the aldehyde **4b** (0.25 g, 0.68 mmol) in methanol (100 mL) was added 10 % Pd/C (100 mg) and hydrogen was bubbled for 2 h The mixture was filtered through celite and the solvent evaporated under vacuum Chromatography of the residue (silica gel, 7:3, petroleum ether diethyl ether) gave 0.15 g (89 %) of *O*-TBNS protected L-(-)-Rhodinose (**2b**) (1:1 : 1.0 mixture of α and β anomers) mp 69-70° C, $[\alpha]_D$ = -13.4 ° (c 1.85, CH_2Cl_2), ^1H NMR (300 MHz, $CDCl_3$) δ 0.065 (s, 6 H, both anomers), 0.92 (s, 9 H, both anomers), 1.12 (d, 3 H, J = 6.6 Hz, α anomer), 1.20 (d, 3 H, J = 6.6 Hz, β anomer), 1.45-2.07 (complex m, 4 H, both anomers), 2.62 (s) and 3.07 (d, J = 7.62 Hz) (OH, both anomers), 3.49 (br dt, 1 H, J = 1.3 Hz, J = 2.8 Hz, β anomer), 3.6 (m, 2 H, both anomers), 4.09 (d q, 1 H, J = 6.6 Hz, J = 1.7 Hz, α anomer), 4.73 (br t, 1 H, β anomer, collapses to d on addition of D_2O), 5.30 (br s, 1 H, α anomer), ^{13}C NMR (75.5 MHz, $CDCl_3$)[24] δ -4.87 (CH_3), -4.64 (CH_3), 17.70 (CH_3), 17.90 (CH_3), 23.90 (#2, α anomer), 25.64 (#3, α anomer)[25a], 25.86 (CH_3), 25.98 (CH_3), 27.49 (#3, β anomer),[25a] 29.82 (q), 30.52 (#2, β anomer), 67.07 (#4, β anomer), 67.41 (#5, α anomer), 68.19 (#4, α anomer),[25b] 74.83 (#5, β anomer),[25b] 92.04 (#1, α anomer), 96.60 (#1, β anomer)

NMR Measurements. The exchangeable protons were removed with D_2O Homonuclear and heteronuclear chemical shift correlation spectra (HOMCOR and HETCOR) were run with standard Varian software

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25. a) and b) In these cases the assignement to α and β anomers might be reversed