Tetrahedron Vol. 46, No. 17, pp. 6167-6184, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

REGIO- AND STEREOSELECTIVE CONJUGATE ADDITION OF NITROGEN NUCLEOPHILES TO 2-ALKENYL *N*-METHYLTHIAZOLIUM IODIDES. SYNTHESIS OF D-3-EPI-DAUNOSAMINE AND SOME LINCOSAMINE ANALOGUES

Alessandro Dondoni,* Giancarlo Fantin, Marco Fogagnolo, and Pedro Merino§

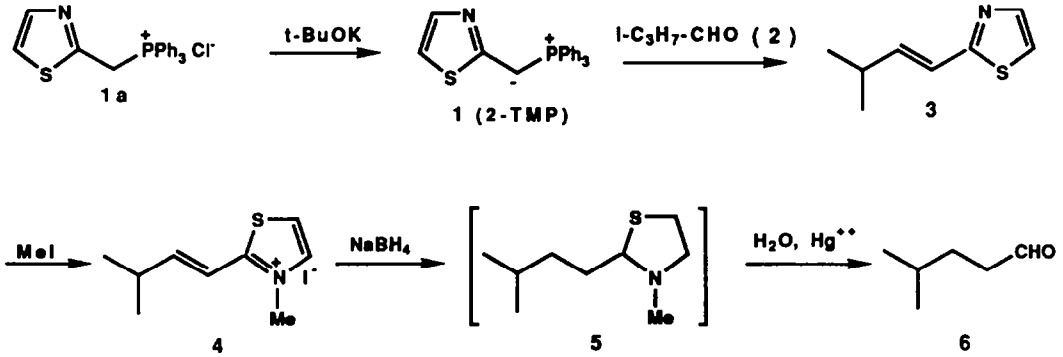
Dipartimento di Chimica, Laboratorio di Chimica Organica, Università, Ferrara, Italy

(*Received in UK* 1 *May* 1990)

Summary : A two-carbon homologation-amination technology of aldehydes is described. Key steps involve the Michael-type addition of a nitrogen nucleophile (benzylamine, trimethylsilylazide, potassium phtalimide) to a 2-alkenyl *N*-methylthiazolium salt obtained by olefination of the aldehyde with the phosphorane (**1**), and the thiazole-to-formyl deblocking. The addition of benzylaminine to the thiazolium salt derived from the acetonide of D-glyceraldehyde occurs with a good level of *syn*-diastereoselectivity (ds, 85-90 %) in agreement with a modified Felkin-Anh model. This technology is employed in short synthetic routes to D-3-*epi*-daunosamine from 4-deoxy D-threose and some lincosamine analogues from α-D-dialdogalactopyranose .

With the aim of developing new synthetic methodologies employing 2-substituted thiazoles (thiazole route[1]) as effective equivalents to aldehydes,[2] we have described the preparation of 2-thiazolylmethylenetriphenylphosphorane (2-TMP, **1**) and its use as a two-carbon homologating reagent of aromatic and aliphatic aldehydes[3a] as well as dialdoses[3b]. Scheme 1 illustrates an application of this methodology to 2-methylpropanal **2**. Key steps are the Wittig-type olefination using **1** generated in situ from the corresponding phosphonium salt **1a**, and the formyl group deblocking from

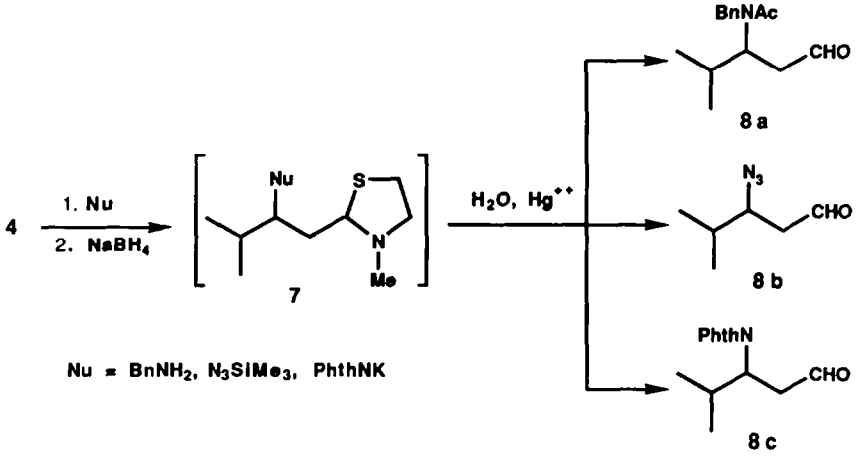
Scheme 1



the thiazole ring in the resulting 2-alkenylthiazole **3** by a one-pot procedure involving *N*-methylation, reduction, hydrolysis. Similarly to that observed for other substrates,[3] the reduction with sodium borohydride of the 2-alkenyl *N*-thiazolium salt **4** occurs both at the heterocyclic ring and at the adjacent carbon-carbon double bond giving the 2-(neopentyl)-thiazolidine **5** which upon mercury-assisted hydrolysis leads to the hexanal **6**. Because of this overreduction, the methology allows to convert an aldehyde into the saturated two-carbon homologue (route A) rather than to the corresponding α,β-enal. This methodology has been conveniently exploited in a short synthesis of the deoxypyranose L-(-)-rhodinose via a differentially protected *syn* 4,5-dihydroxyhexanal as a key intermediate.[4]

We have described the conversion of a 2-alkenylthiazole to a branched saturated aldehyde by addition of an alkyl cuprate[3a] to the ethylenic double bond. Unfortunately, the poor electron-withdrawing character of the 2-thiazolyl group[5], is not sufficient to make 2-alkenylthiazoles good Michael acceptors toward weak nucleophiles such as amines. For instance compound **3** remained unaltered in the presence of excess benzylamine after 48 hours at room temperature. Yet, we sought the amination of 2-alkenylthiazoles an important issue in the context of building up β-amino aldehyde units. A strategy envisioned modifications of the substrate using the *N*-methylthiazolium salt whose superior reactivity as Michael acceptor was foreseen from the very facile addition of the hydride ion in the course of the thiazole-to-formyl deblocking sequence. Thus, we decided to investigated the reaction of **4** with suitable nitrogen nucleophiles (Scheme 2). Treatment of **4** with benzylamine in methanol and then quenching with sodium borohydride gave the thiazolidine **7a** which was characterized by NMR spectroscopy. The acetylation[6] of **7a** and the successive mercury-assisted hydrolysis furnished the *N*-protected β-amino hexanal **8a** in 77 % overall yield. Similarly, the reactions of **4** with trimethylsilylazide and potassium phtalimide provided the corresponding azido and phtalimido substituted aldehydes **8b** (63 %) and **8c** (12 %)[7]. Overall, this process (route B) allows to convert an aldehyde into a two-carbon higher homologue bearing a protected β-amino group which can be liberated under different conditions.[8] This concept should be extensible to the synthesis of various β-functionalized aldehydes using other heteronucleophiles such as alkoxide, phenoxide, and thiophenoxide ions.[9]

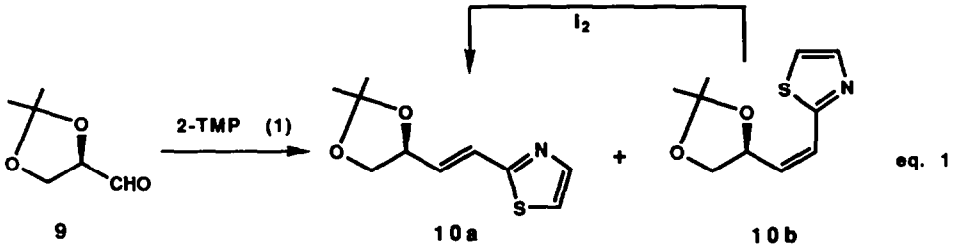
Scheme 2



Synthesis of Amino Sugars. We envisioned application of route B to the construction of chiral β-aminopropanal units toward amino sugars,[10] i.e. a class of compounds owing importance for their role in biological processes and their presence in many important therapeutic agents such as anticancer antibiotics and biopolymers.[11] Recent interest in synthetic strategies to aminosugars has drawn considerable attention to the stereoselective amination of α, β-unsaturated esters and ketones under the influence of an allylic stereocenter.[12] The inter- and intramolecular ring opening of chiral oxiranes with nitrogen nucleophiles[13] constitutes another viable route to amino sugars.

In this paper we explore the suitability of 2-alkenyl thiazolium salts derived from chiral α-alkoxyaldehydes in Michael-type addition to benzylamine and describe the conversion of the adducts into aminopyranoses with five, six, and eight carbon atoms.

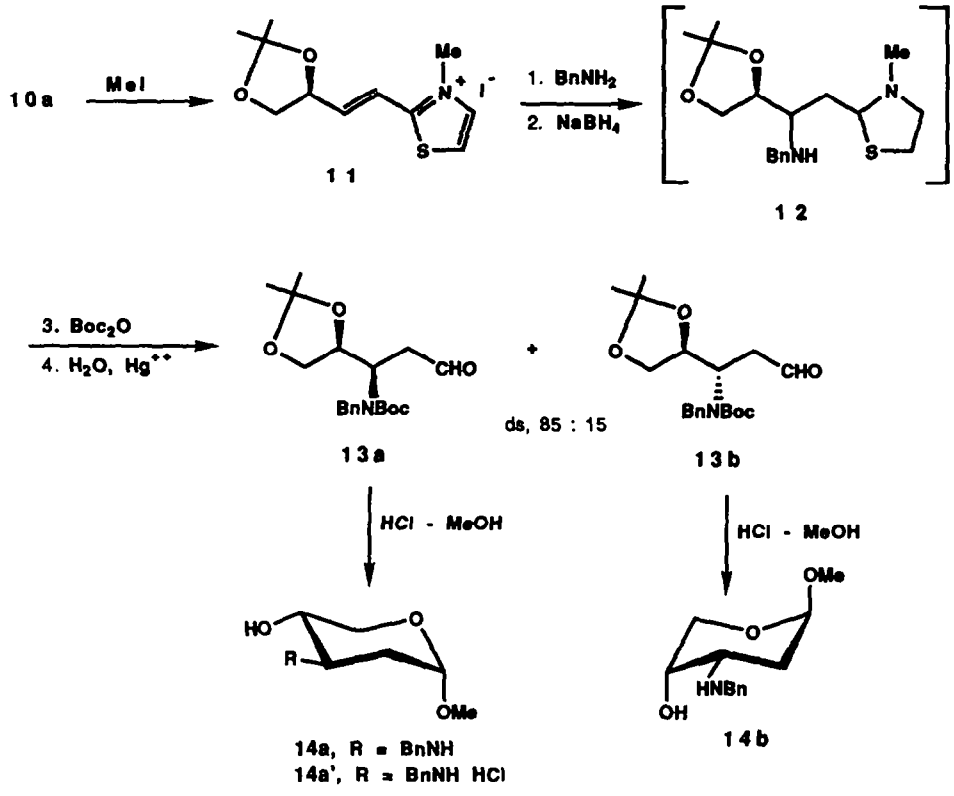
2,3-Dideoxy 3-Aminopentapyranose (14). The readily available enantiomerically pure D-glyceraldehyde acetonide[14] (**9**) appeared to be a convenient starting material for an exploratory study. The olefination of **9** with 2-TMP **1** generated in toluene as described,[3,4] was fairly unselective[15] since a 1 : 1 mixture of E and Z isomers **10a** and **10b** was obtained (eq. 1). This mixture was enriched in the E isomer **10a** (E : Z, 9 : 1) upon refluxing in dichloroethane in the presence of iodine and the pure compounds **10a** and **10b** were separated chromatographically.



9 **10a** **10b**

Since the diasteoselectivity of the Michael addition may vary with the olefin geometry,[15d,f,16] reactions were carried out with a single pure isomer. The E 2-alkenylthiazole **10a** was transformed into the *N*-methylthiazolium iodide **11** in almost quantitative yield by the usual procedure[2] (Scheme 3). Treatment of **11** at -50 °C in methanol[17] with benzylamine and quenching with sodium borohydride produced the thiazolidine **12** as a mixture of diastereoisomers whose ratio could not be determined by NMR as a consequence of the unresolved spectrum. The protection of the benzylamino group of **12** as *N*-Boc derivative using di-tert-butyl dicarbonate (Boc_2O) and the mercury-mediated hydrolysis of the thiazolidine ring gave the aldehydes **13a** and **13b** (80 : 20 ratio , 52 %) which were individually isolated by chromatography. The ratio between **13a** and **13b** gives a rough estimate[18] of the diastereofacial selectivity of the addition of benzylamine to the chiral olefin **11**. The assignment of stereochemistry to the major isomer syn-**13a** based upon a close literature precedent [12b] dealing with the conjugate addition of benzylamine to an α,β-unsaturated ester derived from D-glyceraldehyde acetonide (**9**) as well as upon other examples of amination of γ-alkoxy α,β-unsaturated carbonyl compounds,[12a,c,e] all exibiting high levels of syn-selectivity.[19] The formation of the major adduct syn-**13a** is consistent with a modified Felkin-Ahn type transition state[20] having the allylic alkoxy residue and the medium-sized $-CH_2O-$ group in the anti and inside position respectively and the

Scheme 3



incoming benzylamine attacking the π-system from the less hindered side (anti-periplanar attack) (Figure 1). A similar transition state model has been advanced[10a] for the amination of activated alkenes having alkoxy residues at the allylic stereocenter. Moreover, the preference for the indicated conformation is in agreement with the absence of 1,3-allyl strain[21] due to the little steric interaction between the medium-sized group and the trans-oriented thiazolium ring.

The stereochemistry of **13a** and **13b** was confirmed by analysis of the ^{1}H NMR spectra of pyranoses obtained therefrom. Removal of the isopropylidene and N-Boc protecting groups of **13a** using 8 % hydrochloric acid in anhydrous methanol (Scheme 3) afforded the methyl α-D-threo-pyranoside **14a** ($^4C_1$ ring conformation) which was conveniently characterized through its hydrochloride **14a'**. The complete assignment of ^{1}H NMR signals to **14a'** allowed a straightforward assignment of its stereochemistry. The trans diequatorial orientation (threo configuration) of the OH and NHBn groups is substantiated by the large values of vicinal coupling constants $^3J(2a,3a)$ = 13.5 Hz, $^3J(3,4)$ = 10.5 Hz, and $^3J(4,5a)$ = 11.2 Hz (trans diaxal protons); the stereochemistry at C-1 having the OMe located in an axial orientation due to the anomeric effect[22] is confirmed by $^3J(1,2a)$ = 3.5 Hz and $^2J(1,2e)$ = 1.5 Hz which indicate the absence of a trans diaxial relationship between the protons at C-1 and C-2. Thus the threo configuration at C-3 and C-4 in **14a** confirms the stereochemistry of the major isomer

syn-**13a** and demonstrate the syn selectivity of the addition of benzylamine to the 2-alkenyl thiazolium salt **11**.

In a similar way was the minor isomer anti-**13b** converted to the methyl ß-D-erythro-pyranoside **14b** ($^1C_4$ ring conformation) whose stereochemistry was assigned by the ^1H NMR spectra . Significant data are : $^3J(2a,3)$ = 12.5 Hz and $^3J(3,4)$ = 3.2 Hz proving the cis equatorial-axial orientation of the OH and NHBn groups (erythro configuration); $^3J(1,2e)$ ca. 1 Hz and $^3J(1,2a)$ = 3.2 Hz supporting the axial orientation of the OMe group as expected as a consequence of the anomeric effect.[22] Unfortunately, **14b** was contaminated by an impurity , very likely the α-pyranose tautomer, which prevented the full analytical characterization.

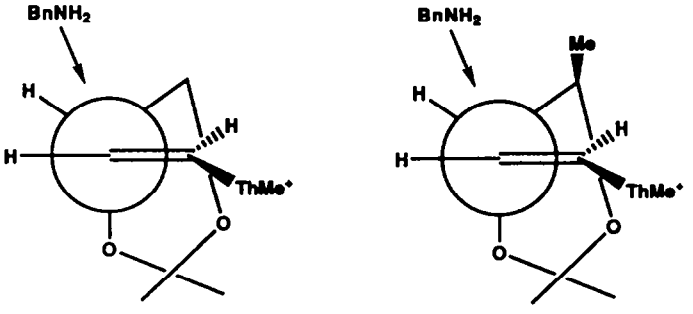
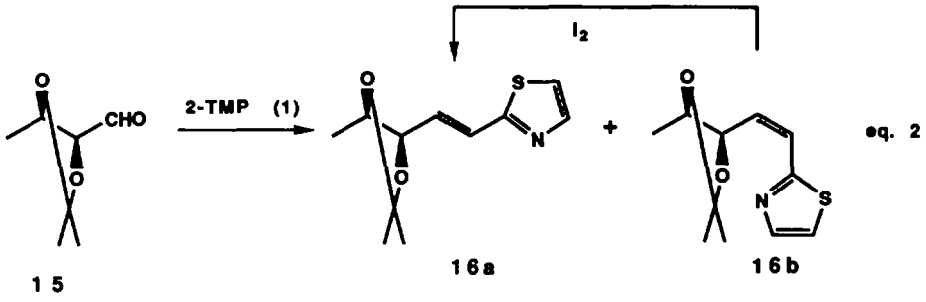


Figure 1. Transition-state models for the addition of benzylamine to chiral 2-alkenyl *N*-methylthiazolium salts **11** (left) and **17** (right)

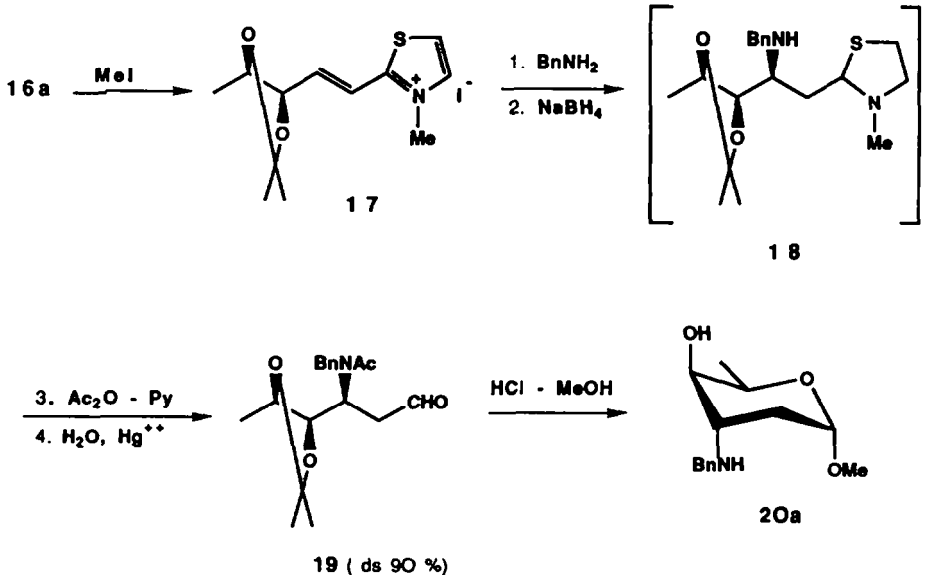
D-3-epi-Daunosamine (20a). 2,3,6-Trideoxy 3-aminohexoses,[23] such as daunosamine, acosamine, ristosamine, vancosamine, etc., are target structures of current interest. The importance of these glycosidic units is due to their presence in anthracycline antitumor antibiotics endowed with considerable activity such as adriamycin, daunomycin, and daunorubicin.[24] Stereochemical modifications at the stereocenters of the amino sugar residue provide some variations of the biological activity of these antibiotics.

We decided to apply the above thiazole-mediated technology to the synthesis of D-3-epi-daunosamine (xylo configuration), i.e. a term of the 2,3,6-trideoxy 3-aminohexose family which has received little attention.[12a,25] To this end, the olefination of 4-deoxy D-threose acetonide[26] (**15**) with the 2-TMP (**1**) and the iodine-catalyzed equilibration of the resulting mixture of E and Z olefins (1 : 1) was employed to prepare the 2-alkenylthiazoles E-(**16a**) and Z-(**16b**) in 9 : 1 ratio (eq. 2). After chromatographic separation , the E isomer **16a** was transformed into thiazolium salt **17** by the usual *N*-methylation procedure (Scheme 4). Treatment of **17** with benzylamine at -50 °C in methanol and processing the reaction mixture as above afforded the protected 2,3,6-trideoxy 3-amino-D-xylohexose (**19**) in good overal yield (63 %) and diastereoselectivity (ds 90 %). The main stereochemical course of the Michael addition to **17** was assigned upon analogy to amination of α,β-unsaturated esters[11a, 25] derived from the aldehyde **15**. This is in agreement with a modified Felkin-Ahn type transition state[20] similar to that suggested for the addition to **11** (Figure 1).



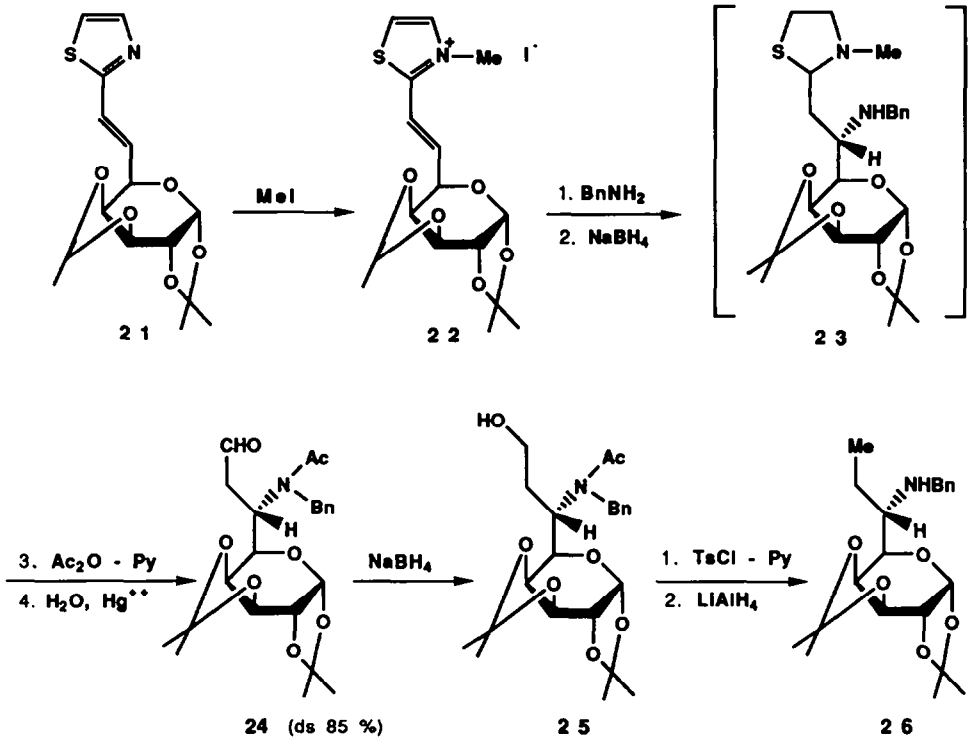
Removal of the isopropylidene and *N*-acetyl protecting groups of **19** with 8 % hydrochloric acid in anhydrous methanol afforded the methyl N-benzyl-α-D-epidaunosaminide (**20a**) (xylo configuration, $^4C_1$ ring conformation) (71%) whose structure followed from the ^1H NMR spectra . Specifically, the relatively small values of vicinal coupling constants allow to exclude the presence of protons with a trans diaxial arrangement. On the other hands, the stereochemistry at C-1 with OMe occupying the axial position for the anomeric effect,[21] is supported by $^3J(1,2a)$ = 3.8 Hz and $^3J(1,2e)$ = 2.4 Hz; moreover the stereochemistry at C-3 with the axial BnNH-group is demonstrated by $^3J(2a,3)$ = 4.7 Hz and $^3J(2e,3)$ = 3.6 Hz. Finally, $^3J(3,4)$ = 4.0 Hz and $^3J(4,5)$ = 1.8 Hz confirm the relative stereochemistry of the groups at C-3, C-4, and C-5 and in particular demonstrate the trans diaxial position of the OH and BnNH-group (threo configuration). Hence, the stereochemistry of **19** and the syn selectivity of the Michael addition of benzylamine to **17** appear to be enough demonstrated. It is important to point out that the NMR data of **20a** compare quite well to those of the known 4-*O*-acetyl 3-acetylamino isomer also existing in the $^4C_1$ conformation.[25]

Scheme 4

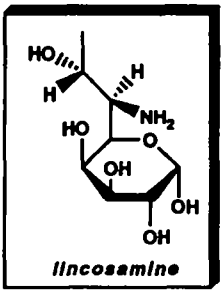


Amino Octoses 24, 25, and 26 : Lincosamine Analogues. In view of the importance of the installation of an aminoalkyl unit at C-5 of a glycosidic moiety in natural product synthesis,[13e] the above homologation-amination technology was applied to the galacto E-eptenepyranoside **21**. This was obtained by the iodine-catalyzed equilibration of the E and Z mixture of alkenes (1 : 3) resulting from the Wittig olefination of the acetonide of α-D-galactodialdopyranose with 2-TMP (**1**) as described.[3b] Also in this case the E alkenylthiazole **21** (Scheme 5) was readily converted into the *N*-methylthiazolium salt **22** which by the one-pot amination-deblocking sequence described above, was transformed into the *N*-protected amino dialdooctose **24** (ds 85 %) in 84 % overal yield . The assignment of the stereochemistry of **24** was less straightforward than in the previous cases due to the lack of literature precedents. Our assignment was based on the assumption that also in this case a modified Felkin-Anh mode of addition[20] is followed, wherein benzylamine attacks the acceptor **22** in the indicated conformation and from the less hindered side, i.e. that opposite to the sugar moiety.

Scheme 5



The aldehyde **24** opens up several possibilities for synthetic elaborations. For instance **24** was reduced to the alcohol **25** (80 %) which upon dehydroxylation afforded the 5-(N-benzylaminopropyl)-pyranoside **26** (69 %). Compounds **25** (6-epi-isolincosamine) and **26** (6-epi-deoxylincosamine) feature structural modifications in the alkylamino group with respect to the amino octose lincosamine[29] which is a component of the commercially important antibiotic lincomycin. Both **25** and **26** are C-6 epimers of lincosamine. Thus a synthetic route to higher amino sugars of biological interest has been achieved.



lincosamine

Conclusions

Schemes 2-5 describe a new methodology for converting an aldehyde into a two-carbon higher homologue having a protected amino group at β position. The key element of the process is the conjugate amination of the 2-alkenylthiazolium salt derived from the aldehyde by Wittig olefination with the thiazole substituted ylide **1**. This reaction occurs very readily and regioselectively due to the strong activating effect of the heteroaryl cation and shows good levels of syn-diastereoselectivity under the influence of an adjacent asymmetric centre. Thus, in addition to the various advantages which are associated with the use of the thiazole molety as a masked formyl group equivalent,[2a] the heterocyclic ring plays a pivotal role as activating group in the heteroconjugate addition. A considerable expansion of the scope of this metholology would be to exert a control on the syn- or anti-orientation of this reaction. Results of our efforts in this direction will be provided in due course. Moreover, the application to the stereospecific synthesis of higher amino sugars using readily available alkenylthiazoles from dialdoses is being actively investigated in our laboratory.

Experimental

General Methods. Melting points are uncorrected. ^{1}H NMR spectra were recorded on a 80 MHz Bruker WP-80 or on a 300 MHz Varian Gemini-300 spectrometer. Chemical shifts are given in parts per million downfield from tetramethylsilane. IR spectra were obtained on a Perkin Elmer Model 297 grating spectrometer. Optical rotations were measured at ca. 22 °C using a Perkin Elmer Model 214

polarimeter. Elemental analyses were performed on a 1106 Microanalyzer (Carlo Erba). Thin layer chromatography on glass-slides precoated with silica gel (Merck Kiesel gel 60 F254) and preparative chromatography on columns of silica gel (Merck 70-230 mesh).

2-Thiazolylmethylenetriphenylphosphonium chloride[3] (**1a**), 3-methyl-1-(2-thiazolyl)-(E)-butene[3a] (**3**), 2,3-O-isopropylidene-D-glyceraldehyde[14] (**9**) 4-deoxy-2,3-O-isopropylidene-D-threose[26] (**15**), 6,7-dideoxy-1,2:3,4-di-O-isopropylidene-7-(2-thiazolyl)-α-D-galacto-ept-6-(E)-ene-1,5-pyranose[3b] (**21**) were prepared as described.

2-(3-methyl)-2-butenyl *N*-Methylthiazolium Iodide (4). A solution of the vinylthiazole 3 (2.2 g, 14.4 mmol) and methyl iodide (20.16 g, 144 mmol) in acetonitrile (80 ml) was refluxed for 6 h. The solvent was partially removed under vacuum and ethyl ether (50 ml) was added. The precipitate was filtered and washed several times with cold ethyl ether to give 3.7 g (87 %) of the pure salt 4. Red solid; mp 116-117 °C; ^{1}H NMR (Acetone-d_6 80 MHz) δ 8.48 (d, 1H, J = 3.7 Hz), 8.20 (d, 1H, J = 3.7 Hz), 7.21 (m, 2H), 4.38 (s, 3H), 2.08 (m, 1H), 1.19 (d, 6H, J = 6.4 Hz).

Anal. Calcd for $C_9H_{14}INS$: C, 36.62; H, 4.78; N, 4.75. Found: C, 36.37; H, 4.61; N, 4.93.

4-Methylpentanal (6). The thiazolium salt 4 (0.8 g, 2.71 mmol) was treated with sodium borohydride (0.15 g, 4.1 mmol) in methanol at 0 °C under stirring. After additional 20 min stirring at room temperature, acetone (1 ml) was added and the solvent distilled under reduced pressure. The residue was treated with an aqueous saturated solution of sodium bicarbonate (20 ml) and extracted with methylene chloride (2 x 30 ml). Organic layer was dried over anhydrous sodium sulfate and the solvent evaporated to yield the crude thiazolidine 5, which was dissolved in 3 ml of acetonitrile and added dropwise to a solution of mercuric chloride (0.95 g, 3.5 mmol) in 30 ml of acetonitrile-water (4:1). The mixture was stirred for 15 min, filtered and partitioned between pentane (2 x 30 ml) and brine (30 ml). The evaporation of pentane gave 0.11 g (42%) of the aldehyde 6 as a volatile liquid (litt.[29] b.p. 121° C); IR (film) ν 1715; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 9.68 (t, 1H, J = 1.6 Hz), 2.40 (m, 2H), 1.53 (m, 3H), 0.90 (d, 6H, J = 7.0 Hz).

***N*-Acetyl-*N*-benzyl-3-amino-4-methylpentanal (8a).** To a solution of 0.8 g (2.71 mmol) of the thiazolium salt 4 in anhydrous methanol (30 ml) at room temperature were added 0.38 g (3.55 mmol) of freshly distilled benzylamine and the reaction mixture was stirred for 4 h. Then 0.15 g (4.1 mmol) of sodium borohydride were added portionwise at 0 °C. After stirring for 15 min, 1 ml of acetone was added and the solvent was distilled under reduced pressure. The residue was treated with an aqueous saturated solution of sodium bicarbonate (20 ml) and extracted with methylene chloride (2 x 30 ml). After drying over anhydrous sodium solfate, the solvent was evaporated in vacuo to give the crude β-aminoalkylthiazolidine 7. The crude product was dissolved in 2 ml of pyridine and 1 ml of acetic anhydride was added. After 4 h the solvent was removed under high vacuum and the residue was partitioned between methylene chloride (2 x 30 ml) and aqueous sodium bicarbonate. The organic layer

was dried over sodium sulfate and concentrated in vacuo to yield the corresponding N-acetyl derivative which was dissolved in 3 ml of acetonitrile and added dropwise to a solution of mercuric chloride (0.95 g, 3.5 mmol) in 30 ml of acetonitrile-water (4 : 1). The mixture was stirred for 15 min, filtered and the solvent evaporated. The residue was treated with brine (30 ml) and then extracted with methylene chloride (2 x 30 ml); the organic layer was dried over sodium sulfate, concentrated in vacuo, and filtered through a bit of silica gel, using 50:50 methylene dichloride-petroleum ether to yield the aldehyde **8a** (0.51 g, 77 %). Oil; IR (film) υ 1715, 1650; ^{1}H NMR ($CDCl_3$ 333 K, 80 MHz) δ 9.53 (br s 1H), 7.28 (m, 5H), 4.59-4.09 (m, 4H), 2.69 (m, 1H), 2.58 (m, 1H), 2.19 (s, 3H), 1.0 (d, 3H, J=2.2 Hz), 0.91 (d, 3H, J=2.4 Hz).

Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.81; H, 8.59; N, 5.82.

3-Azido-4-methylpentanal (8b). The thiazolium salt **4** (O.8 g, 2.71 mmol) was treated sequentially with trimethylsilyl azide (0.41 g, 3.55 mmol), sodium borohydride (0.15 g, 4.1 mmol) and mercuric chloride (0.95 g, 3.5 mmol) as described above. The resulting material was chromatographed through a short column (silica gel, 50:50 petroleum ether-diethyl ether) to give 0.24 g (63%) of the aldehyde **8b**. Oil; IR (film) υ 2080, 1715; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 9.76 (t, 1H, J=1.3 Hz), 3.76 (br q, 1H, J=6 Hz), 2.64 (m, 1H), 2.56 (d, 1H, J=1.3 Hz), 1.76 (m, 1H), 0.99 (d, 3H, J=6.7 Hz), 0.97 (d, 3H, J=6.7 Hz).

Anal. Calcd for $C_6H_{11}N_3O$: C, 51.05; H, 7.85; N, 29.76. Found: C, 51.09; H, 8.00; N, 29.72.

4-Methyl-3-phtalimidopentanal (8c). The thiazolium salt **4** (O.8 g, 2.71 mmol) was treated sequentially with potassium phtalimide (0.66 g, 3.55 mmol), sodium borohydride (0.15 g, 4.1 mmol) and mercuric chloride (0.95 g, 3.5 mmol) as described above. The resulting material was chromatographed through a short column (silica gel, 50:50 petroleum ether-diethyl ether) to give 0.08 g (12%) of the aldehyde **8c**. Oil; IR (film) υ 1770, 1715, 1700; ^{1}H NMR ($CDCl_3$, 80 MHz) δ 9.68 (brs, 1H), 7.68 (m, 4H), 4.40 (dt, 1H, J = 10.1 Hz, J = 4.4 Hz), 3.40 (ddd, 1H, J = 17.5 Hz, J = 10.1 Hz, J = 1.9 Hz), 2.87 (dd, 1H, J=17.5 Hz, J = 4.4 Hz), 2.34 (m, 1H), 1.03 (d, 3H, J = 6.7 Hz), 0.87 (d, 3H, J = 6.7 Hz).

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.39; H, 6.15; N, 5.95.

(3S)-*O*-Isopropylidene-3,4-dihydroxy-1-(2-thiazolyl)-1-butene (10). To a stirred suspension of the phosphonium salt **1a** (8.20 g, 20.7 mmol) in anhydrous toluene (80 ml) was added potassium tert-butoxide (2.32 g, 20.7 mmol) and the mixture was stirred at room temperature for 2 h. To the reaction mixture was added dropwise a solution of D-glyceraldehyde acetonide (9) (2.96 g, 22.8 mmol) in toluene (15 ml). After additional stirring at room temperature for 15 h, the solvent was distilled under reduced pressure and the residue was treated with petroleum ether (150 ml). The mixture was filtered through celite and the filtrate was concentrated in vacuo to give the alkene **18** (3.9 g) as a mixture of E and Z isomers in 56 : 44 ratio by ^{1}H NMR . A solution of this mixture (3.3 g) and a few crystals of iodine in 1,2-dichloroethane was refluxed for 40 h (TLC monitoring). The resulting red solution was washed with a sodium tiosulfate solution, dried (Na_2SO_4), and the solvent

evaporated under reduced pressure. Chromatography of the residue (silica gel, 70:30 petroleum ether-diethyl ether) afforded 3.16 g (72%) of the E-isomer (**10a**) and 0.35 g (8%) of Z-isomer (**10b**).

10a: oil; $[\alpha]_D$ = +54.6° (c 2.71, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.72 (d, 1H, J = 3.2 Hz), 7.21 (d, 1H, J = 3.2 Hz), 6.92 (d, 1H, J = 16.0 Hz), 6.50 (dd, 1H, J = 16.0 Hz, J = 6.2 Hz), 4.70 (m, 1H), 4.19 (dd, 1H, J = 8.4 Hz, J = 6.4 Hz), 3.71 (dd, 1H, J = 8.4 Hz, J = 7.2 Hz)1.47 (s, 3H), 1.43 (s, 3H).

Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found: C, 56.71; H, 6.17; N, 6.67.

10b: oil; $[\alpha]_D$ = +134.6° (c 1.39, CH_2Cl_2); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.78 (d, 1H, J = 3.2 Hz), 7.27 (d, 1H, J = 3.2 Hz), 6.60 (m, 1H), 6.05 (dd, 1H, J = 11.2 Hz, J = 7.2 Hz), 5.60 (m, 1H), 4.45 (dd, 1H, J = 8.4 Hz, J = 6.4 Hz), 3.66 (dd, 1H, J = 8.4 Hz, J = 6.8 Hz),1.47 (s, 3H), 1.43 (s, 3H).

Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.85; H, 6.20; N, 6.63. Found: C, 58.93; H, 6.36; N, 6.40.

2-Alkenyl *N*-Methylthiazolium Iodide (11). A solution of the E 2-alkenylthiazole **10a** (3 g, 14.2 mmol) and methyl iodide (20 g, 142 mmol) in methanol was refluxed until total consumption of the olefin by TLC (ca. 12 h). The solvent was removed under vacuum to give the thiazolium salt 11 as a syrup in practically quantitative yield. The crude material was washed several times with anhydrous diethyl ether and used without further purification. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.66 (d, 1H, J = 3.8 Hz), 8.32 (d, 1H, J = 3.8 Hz), 7.23 (d, 1H, J = 15.7 Hz), 7.13 (dd, 1H, J = 15.7 Hz, J = 4.5 Hz), 4.97 (m, 1H), 4.37 (s, 3H), 4.35 (m, 1H,), 3.88 (dd, 1H, J = 8.6 Hz, J = 6.7 Hz),1.50 (s, 3H), 1.42 (s, 3H).

Addition of Benzylamine to the Thiazolium Salt (11). To a solution of 4.9 g (14 mmol) of **11** in anhydrous methanol (60 ml) at -50 °C were added 1.95 g (18.2 mmol) of benzylamine. After 4 hours stirring, 0.79 g (21 mmol) of sodium borohydride were added portionwise and the mixture was allowed to warm to 0 °C. Acetone (2 ml) was added and the solvent was evaporated under reduced pressure. The residue was treated with a saturated solution of sodium bicarbonate (30 ml) and the mixture was extracted with methylene chloride (3 x 40 ml). The combined organic layers were dried over magnesium sulfate and the solvent evaporated under reduced pressure to give the thiazolidine **12** as a yellow oil. The ^1H NMR spectrum of this material did not show resonances corresponding to the 4H and 5H of the thiazole ring (δ 8.66 and 8.32 ppm) as well as to the ethylenic protons (δ 7.23 and 7.13).

The crude thiazolidine **12** was dissolved in dioxane (40 ml), cooled in an ice bath and treated with 3.66 g (16.8 mmol) of Boc_2O. After 20 min at 5 °C and 5 hours at room temperature, the mixture was concentrated, treated with a saturated solution of sodium bicarbonate (20 ml) and extracted with methylene chloride (3 x 30 ml). The combined extracts were dried over magnesium sulfate and the solvent evaporated to give the *N*-Boc derivative as an oil.

This material was dissolved in 5 ml of acetonitrile and slowly added to a solution of mercuric chloride (4.9 g, 18.2 mmol) in 50 ml of acetonitrile-water (4:1). The mixture was stirred for 15 min., filtered and the solvent evaporated. The residue was treated with 30 ml of brine, and extracted

several times with methylene chloride. The organic layers were combined, dried over magnesium sulfate, and the solvent evaporated under reduced pressure. Chromatography of the residue over silica gel using petroleum ether-diethyl ether (70:30) as eluent afforded the individual aldehydes **13a** (syn adduct) (2.1 g, 42%) and **13b** (anti adduct) (0.53 g, 10%).

13a: oil; $[\alpha]_D$ = +33.9° (c 1.55, $CHCl_3$); IR (film) υ 1725, 1685; ^1H NMR ($CDCl_3$ 333 K, 80 MHz) δ 9.37 (t, 1H, J = 1.8 Hz), 7.18 (s, 5H), 4.50 (s, 2H), 4.37-3.48 (m, 4H), 2.70 (m, 2H), 1.45 (s, 9H), 1.37 (s, 3H), 1.28 (s, 3H).

Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 66.09; H, 8.04; N, 3.85. Found: C, 66.19; H, 8.12; N, 4.05.

13b: oil; $[\alpha]_D$ = +1.5° (c 4.15, $CHCl_3$); IR (film) υ 1720, 1685; ^1H NMR ($CDCl_3$ 333 K, 80 MHz) δ 9.53 (t, 1H, J=2.1 Hz), 7.18 (s, 5H), 4.37 (s, 2H), 4.21 (m, 2H), 3.59 (m, 2H), 2.73 (m, 2H), 1.45 (s, 9H), 1.32 (s, 3H), 1.23 (s, 3H).

Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 66.09; H, 8.04; N, 3.85. Found: C, 65.95; H, 8.07; N, 3.92.

Methyl 2,3-Dideoxy-3-*N*-Benzylamino-α-D-*threo*-penta-1,5-pyranoside (14a). A solution of the aldehyde **13a** (1 g, 2.75 mmol) in 40 ml of 8% HCl in anhydrous methanol was stirred at room temperature for 12 h. After evaporation of the solvent under reduced pressure, the residue was treated with petroleum ether-diethyl ether (80:20) and then filtered to give 0.67 g (90%) of the hydrochloride **14a'** as a white solid; mp 170 °C (dec); $[\alpha]_D$ = +54.3° (c 0.66, CH_3OH); ^1H NMR (D_2O, 300 MHz) δ 7.30 (s, H_{arom}), 4.76 (m, H_{1e}), 4.15 (AB quartet, CH_2Ph), 3.70 (m, H_{3a}), 3.59 (m, H_{5e}), 3.30 (m, H_{5a}), 3.22 (m, H_{3a}), 3.15 (s, OCH_3), 2.20 (ddd, H_{2e}), 1.74 (dt, H_{2a}). $J_{1e,2a}$ = 3.5, $J_{1e,2e}$ = 1.5, $J_{2a,2e}$ = 13.5, $J_{2a,3a}$ = 13.5, $J_{2e,3a}$ = 4.8, $J_{3a,4a}$ = 10.5, $J_{4a,5e}$ = 6.0, $J_{4a,5a}$ = 11.2, $J_{5a,5e}$ = 11.2, $J_{AB(CH_2Ph)}$ = 13.2. ^{13}C NMR (D_2O, 75.5 MHz) δ 137.64 (s), 136.84 (d), 136.48 (d), 103.63 (d), 72.71 (d), 68.22 (t), 62.35 (t), 61.25 (q), 55.2 (t), 37.28 (t).

Anal. Calcd for $C_{13}H_{20}ClNO_3$: C, 57.03; H, 7.36; N, 5.11. Found: C, 57.23; H, 7.39; N, 5.07.

A suspension of the hydrochloride **14a'** (0.3 g) in an aqueous saturated solution of sodium bicarbonate (10 ml) was stirred vigorous and then extracted with ethyl acetate (2 x 10 ml). The usual work-up gave **14a** in a virtually quantitative yield as a syrup which crystallized on standing for several days; m.p. 72-74 °C (methylene chloride - petroleum ether), $[\alpha]_D$ = +30.1° (c 4.5, $CHCl_3$); ^1H NMR ($CDCl_3$ + D_2O, 300 MHz) δ 7.35 (m, 5H), 4.78 (m, 1H), 3.80 (AB quartet, J = 12.8 Hz), 3.62 (m, 1H), 3.48 (m, 2H), 3.34 (s, 3H), 2.91 (ddd, 1H, J = 11.8 Hz, J = 9.0 Hz, J = 4.3 Hz), 2.25 (ddd, 1H, J = 13.2 Hz, J = 4.3 Hz, J = 1.5 Hz), 1.42 (ddd, 1H, J = 13.2 Hz, J = 11.8 Hz, J = 3.6 Hz).

Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.85; H, 7.90; N, 6.0

Methyl 2,3-Dideoxy-3-*N*-Benzylamino-α-D-*erythro*-penta-1,5-pyranoside (14b). The aldehyde **13b** (0.4 g, 1.1 mmol) was dissolved in 25 ml of 8% HCl in anhydrous methanol and the solution stirred at room temperature for 12 h. After evaporation of the solvent under reduced pressure the residue was suspended in an aqueous saturated solution of sodium bicarbonate (10 ml), the mixture

stirred vigorously, and then extracted with ethyl acetate (2 x 10 ml). The organic layers were combined, dried with magnesium sulfate, and the solvent vaporated under reduced pressure to give 0.24 g (80%) of **14b** as a syrup containing ca. 10% of non removable impurity : ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32 (s, H_{arom}), 4.77 (m, H_{1e}), 4.94-4.65 (m, H_{4e}, H_{5a}, H_{5e}, NH, OH, CH_2Ph), 3.35 (s, OCH_3), 3.12 (m, H_{3a}), 1.81 (m, H_{2e}), 1.67 (m, H_{2a}). $J_{1e,2e}$≈1.0, $J_{1e,2a}$ = 3.2, $J_{2a,2e}$ = 12.5, $J_{2e,3a}$ = 5.0, $J_{2a,3a}$ = 12.5, $J_{3a,4e}$ = 3.2.

(3R,4R)-*O*-Isopropylidene-3,4-dihydroxy-1-(2-thiazolyl)-1-pentene (16). The reaction between 2,3-*O*-isopropylidene-4-deoxy-D-threose (**13**) (3.7 g, 26.9 mmol) and the phosphonium chloride **1a** (9.70 g, 24.5 mmol) was carried out as described above for D-glyceraldehyde acetonide **9**. After the iodine-catalyzed equilibration of the crude mixture of E and Z olefins (57 : 43), chromatography (silica gel, 70 : 30 petroleum ether-diethyl ether) gave 4.03 g (73 %) of the E isomer **16a** and 0.44 g (8 %) of Z isomer **16b**.

16a: oil; $[\alpha]_D$ = -11.2° (c 2.44, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.76 (d, 1H, J = 3.2 Hz), 7.23 (d, 1H, J = 3.2 Hz), 6.95 (d, 1H, J = 15.6 Hz), 6.50 (dd, 1H, J = 15.6 Hz, J = 6.0 Hz), 3.77-4.25 (m, 2H), 1.45 (s, 6H), 1.32 (d, 3H, J = 6.0 Hz).

Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.52; H, 6.91; N, 6.35.

16b: oil; $[\alpha]_D$ = -58.5° (c 4.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 (d, 1H, J = 3.2 Hz), 7.32 (d, 1H, J = 3.2 Hz), 6.78 (d, 1H, J = 11.8 Hz), 5.85 (dd, 1H, J = 11.8 Hz, J = 8.8 Hz), 5.31 (m, 1H), 3.72-4.10(m, 1H), 1.46 (s, 6H), 1.35 (d, 3H, J = 6.2 Hz).

Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.73; H, 6.95; N, 6.11.

2-Alkenyl *N*-Methylthiazolium Iodide (17). The reaction was carried out as for compound **11** starting from the E-olefin **16a** (2.5 g, 11.1 mmol). The crude salt (**17**) isolated as a sticky syrup as described above showed the following : ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68 (d, 1H, J = 3.6 Hz), 8.37 (d, 1H, J = 3.6 Hz), 7.21 (d, 1H, J = 15.7 Hz), 7.06 (dd, 1H, J = 15.7 Hz, J = 4.9 Hz), 4.36 (s, 3H), 4.34 (m, 1H), 4.0 (m, 1H), 1.47 (m, 9H).

Addition of Benzylamine to the Thiazolium Salt (17). The salt (**17**) (3.5 g, 9.5 mmol) was treated with benzylamine (1.32 g, 12.3 mmol) and reduced with sodium borohydride (0.54 g, 14.2 mmol) as described for **11**. The resulting crude thiazolidine **18** was acetylated by treatment with 2.5 ml of acetic anhydride, 5 ml of pyridine and a catalityc amount of 4-dimethylamino pyridine. After 12 h stirring at room temperature the solvent was removed in vacuo. The residue was treated with an aqueous saturated solution of sodium bicarbonate (20 ml) and extracted with methylene chloride (3 x 30 ml). The usual work-up gave an oil which upon treatment with mercuric chloride (3.3 g, 12.3 mmol) as described above, followed by chromatography over silica gel (80 : 20 diethyl ether-petroleum ether as an eluent) gave the aldehyde **19** (1.91 g, 63%) in 90% diastereomeric purity by NMR; IR (film) ν 1715, 1640; ^{1}H NMR ($CDCl_3$, 80 MHz) δ (9.57 (brs, 0.7 H), 9.21 (brs, 0.3 H))(collapsed to singlet,

1H at 333 K), 7.31 (m, 5H), 5.21 (m, 1H), 4.81 (m, 1H), 4.53 (m, 1H), 3.79 (m, 1H), 2.78 (m, 2H), 2.09 (s, 3H), 1.35 (m, 9H).

Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.96; H, 7.83; N, 4.16.

Methyl *N*-Benzyl-α-D-3-epi-Daunosaminide (20a). The aldehyde **19** (1.5 g, 4.7 mmol) was dissolved in 50 ml of a cooled 8% HCl solution in anhydrous methanol. After overnight stirring at room temperature and evaporation of the solvent under reduced pressure, the residue was suspended in a saturated solution of sodium bicarbonate (20 ml) and extracted with ethyl acetate (2 x 30 ml). The combined organic layers were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Silica gel chromatography using 70 : 30 diethyl ether-ethyl acetate as the eluent gave 0.84 g (71%) of **20a** as a syrup; $[\alpha]_D$ = +93.8° (c 1.725, $CHCl_3$); ^1H NMR (DMSO-d_6, 300 MHz) δ 7.30 (m, H_{arom}), 4.62 (d, OH), 4.59 (m, H_{1e}), 3.94 (dq, H_{5a}), 3.73 (AB quartet, CH_2Ph), 3.32 (br, NH), 3.29 (m, H_{4e}), 3.20 (s, OCH_3), 2.61 (m, H_{3e}), 1.93 (m, H_{2a}), 1.50 (m, H_{2e}), 1.07 (d, CH_3). $J_{1e,2a}$ = 3.8, $J_{1e,2e}$ = 2.4, $J_{2a,2e}$ = 13.9, $J_{2a,3e}$ = 4.7, $J_{2e,3e}$ = 3.6, $J_{3e,4e}$ = 4.0, $J_{4e,5a}$ = .8, $J_{4e,OH}$ = 5.6, J_{5a,CH_3} = 6.7. ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 141.27 (s), 129.14 (d), 128.83 (d), 127.85 (d), 99.62 (d), 71.0 (d), 62.43 (d), 55.50 (q), 54.90 (d), 51.88 (t), 28.05 (t), 16.65 (q).

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57. Found: C, 67.06; H, 8.37; N, 5.54.

2-Alkenyl *N*-Methylthiazolium Iodide (22). A solution of the (E)-ene sugar **21** (O.61g,1.33 mmol) and methyl iodide (0.88 ml,14 mmol) in 10 ml of acetonitrile was refluxed for 12 hours. The evaporation of the solvent under reduced pressure and addition of 25 ml of diethyl ether gave a solid material which was filtered and washed several times with cold diethyl ether. This crude material was crystallized from methanol-diethyl ether to give O.78 g (98%) of the pure salt **22**: mp 77-79 °C ; $[\alpha]_D$ = -138.1° (c 1.0, MeOH); ^1H NMR (CD_3OD, 300 MHz) δ 7.42 (d, 1H, J=4.1 Hz), 7.26 (d, 1H, J = 4.1 Hz), 6.37 (m, 2H), 4.85 (d, 1H, J = 4.9 Hz), 3.93 (m, 2H), 3.69 (m, 2H), 2.51 (m, 2H), 0.74 (s, 3H), 0.60 (s, 3H), 0.57 (s, 3H), 0.54 (s, 3H).

Anal. Calcd for $C_{17}H_{17}INO_5S$: C, 42.42; H, 5.03; N, 2.91. Found: C, 42.28; H, 5.13; N, 2.93.

(6S)-*N*-Acetyl-*N*-benzyl-6-amino-6,7-Dideoxy-1,2:3,4-di-O-isopropylidene-α-D-galacto-octodialdo-1,5-pyranose (24). The thiazolium salt **22** (O.64 g,1.06 mmol) in 40 ml of anhydrous methanol was treated with benzylamine (0.19 g, 1.78 mmol) and then with sodium borohydride (0.09 g, 2.37 mmol) as described for compound **11**. The crude thiazolidine **23** was acetylated by treatment with 2 ml of freshly distilled pyridine, 1.5 ml of acetic anhydride, and a catalytic amount of dimethylamino pyridine. After stirring overnight at room temperature, the solvent was distilled under reduced pressure and the residue was treated with 30 ml of a saturated solution of sodium bicarbonate and extracted with ethyl acetate (3 x 30 ml). The solvent was distilled in vacuo and the residue treated with mercuric chloride (0.65 g, 2.4 mmol) under the conditions described for **11**. The usual work-up gave the crude dialdose **24** (ds = 85% by NMR)) which was purified by a silica gel column chromatography (eluent, 20:80 petroleum ether-diethyl ether) : 0.34 g (84%,); oil; $[\alpha]_D$ = -38.5° (c 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$ 333 K, 80 MHz) δ 9.38 (br s, 1H), 7.23 (m, 5H), 5.36 (d,

1H, J = 5.1 Hz), 4.66-4.03 (m, 6H), 2.75 (m, 1H), 2.18 (m, 2H), 2.09 (s, 3H), 1.5 (s, 3H), 1.38(s, 3H), 1.22 (br s, 6H).

Anal. Calcd for $C_{23}H_{31}NO_7$: C, 63.73; H, 7.21; N, 3.23. Found: C, 63.43; H, 7.27; N, 3.17.

(6S)-*N*-Acetyl-*N*-benzyl-6-amino-6,7-Dideoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galacto-octulo-1,5-pyranose (25). To a solution of the dialdose **24** (O.3g ,0.693 mmol) in 25 ml of methanol, cooled in an ice bath, was added portionwise sodium borohydride (60 mg, 1.58 mmol), and stirring was continued until the complete disappearance of the starting material by TLC (eluent 10 : 90 petroleum ether-ethyl ether). The solvent was rotatory evaporated and the residue was treated with 20 ml of brine and extracted with methylene chloride (3 x 30 ml). Organic layers were combined, dried over anhydrous sodium sulfate, filtered and the solvent evaporated in vacuo. Column chromatography of the residue (silica gel, 10 : 90 petroleum ether-ethyl ether) gave the pure octulose **25**, 250 mg (80%) as a sticky solid : mp 66-68 °C; $[\alpha]_D$ = -49.3° (c 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (m, 5H), 5.53 (d, 1H, J = 5.1 Hz), 4.73-4.20 (m, 7H), 3.83 (m, 1H), 3.67 (m, 1H), 3.49 (m, 2H), 3.73 (br s, 1H, ex D_2O), 2.23 (m, 3H), 1.63-1.30 (m, 12 H).

Anal. Calcd for $C_{23}H_{33}NO_7$: C, 63.43; H, 7.64; N, 3.22. Found: C, 63.21; H, 7.53; N, 3.56.

***N*-Benzyl-7-deoxy-6-epi-1,2:3,4-di-*O*-isopropylidene-lincosamine (26).** To a solution of **25** (225 mg ,0.52 mmol) in 5 ml of freshly distilled pyridine, cooled in an ice-bath, was added p-toluenesulphonyl chloride (120 mg, 0.6 mmol) and the mixture was stirred at room temperature for 12 hours. The pyridine was distilled in vacuo vacuo, the residue was treated with a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, the solvent was evaporated and the resulting crude tosylate dissolved in 20 ml of anhydrous tetrahydrofuran was added to a suspension of 41 mg (1.04 mmol) of lithium aluminium hydride in 10 ml of the same solvent. After stirring for 2 hours, water was added carefully (three drops), the mixture filtered and the solvent evaporated. The residue was treated with 30 ml of a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate (3 x 30 ml). The combined organic layers, dried over anhydrous sodium sulfate and evaporation of the solvent, gave a crude material which by column chromatography (silica gel, 50 : 50 ethyl acetate-diethyl ether) afforded 136 mg (69 %) of the amino sugar **26** : oil; $[\alpha]_D$ = -33.6° (c 0.85, $CHCl_3$).; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.28 (m, 5H), 5.62 (d, 1H, J = 4.8 Hz), 4.60 (dd, 1H, J = 2.2 Hz, J=7.4 Hz), 4.33 (dd, 1H, J = 2.4 Hz, J = 2.4 Hz), 4.14 (dd, 1H, J = 1.7 Hz, J = 7.2 Hz), 3.95-3.66 (m, 3H), 3.50 (m, 1H), 3.22 (m, 1H), 2.81 (m, 1H), 2.62 (m,1H), 1.46 (s,3H), 1.44 (s,3H), 1.36 (s,3H), 1.30 (s,3H), 1.02 (t, 3H, J = 7.1 Hz).

Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.65; H, 8.15; N, 3.60.

Acknowledgment : Work supported by Progetto Finalizzato di Chimica Fine e Secondaria (CNR, Rome).

References and Notes

§ Postdoctoral Research Associate on Grant PF 89-17871707 from the Ministerio de Educacion y Ciencia (Spain).

1. Thiazole Route to Carbohydrates : Synthesis of building blocks or precursors to carbohydrates and related compounds using functionally substituted thiazoles. For recent accounts see : Dondoni, A. *Phosphorus, Sulfur, and Silica* **1989**, *43*, 25. Dondoni, A. *Pure and Applied Chemistry* **1990**, *62*, 643.
2. See for instance : a) 2-(trimethylsilyl)thiazole as an equivalent to CHO^- (Dondoni, A.; Fantin, G. ; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693. Dondoni, A.; Fantin, G. ; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1990**, *55*,1439). b) 2-thiazolylcarbonitrile N-oxide as an equivalent to OHC-CNO (Dondoni, A.; Fantin, G. ; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron* **1988**, *44*, 3215) . c) 2-(acetyl)thiazole as an equivalent to $^-CH_2$-CH(OH)-CHO (Dondoni, A.; Fantin, G. ; Fogagnolo, M. *Tetrahedron Lett.* **1989**, *30*, 6063).
3. a) Dondoni, A.; Fantin, G. ; Fogagnolo, M.; Medici, A.; Pedrini, P. Tetrahedron, 1988, 44, 2121. b) Dondoni, A.; Fantin, G. ; Fogagnolo, M.; Merino, P. *J. Carbohydr. Chem.* **1990**, in press.
4. Dondoni, A.; Fantin, G. ; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron* **1989**, *45*, 5141.
5. Noyce, D. S.; Fike, S. T. *J. Org. Chem.* **1973**, *38*, 3316.
6. The mercury-mediated hydrolysis of the thiazolidine ring to the formyl group does not tolerate a free amino group. The conversion to an amidic function such as *N*-Boc (ref. 2a) or *N*-Acetyl (Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Tetrahedron* **1988**, *44*, 3215) overcomes this problem.
7. The low isolated yield of **8c** asks for modified conditions to make this functionalization synthetically useful.
8. Green, T. W. 'Protective Groups in Organic Chemistry,' Wiley, New York, 1981. See also : a) For $PhCH_2NH_2$ to $-NH_2$ see : Carcano, M.; Nicotra, F.; Panza, L.; Russo, G. *J. C. S., Chem. Commun.* **1989**, 297. b) For PhthN- to $-NH_2$ see: Motawia, M. S.; Wengel, J.; Abdel-Megid, A. E.-S. ; Pedersen, E. B. *Synthesis* **1989**, 384. c) For $-N_3$ to $-NH_2$ see : Sarma, J. C. ; Sharma, R. P. *Chem. Ind. (London)* **1987**, 764 ; d) for $-N_3$ to NH-Boc see : Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Letters* **1989**, *30*, 837.
9. Results from our ongoing work in this area will be published in due course.
10. For various synthetic routes to amino sugars from non-carbohydrate precursors see : a) McGarwey, G. J.; Kimuea, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125. b) Hauser, F. M. ; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35. c) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. See also ref. 2 and 4.
11. Horton, D.; Wander, J. D. in 'The Carbohydrates', Pigman, W.; Horton, D. ; Eds., Academic Press, New York, 1980, vol. 1B, ch. 16. Kennedy, J. F.; White, C. A., 'Bioactive Carbohydrates', Ellis Horwood, Ltd.; Chichester, West Sussex, 1983.
12. a) Fronza, G.; Fuganti, C.; Grasselli, P.; Marinoni, G. *Tetrahedron Lett.* **1979**, 3883. b) Matsunaga, H.; Sakamaki, T.; Nagaoka, H.; Yamada, Y. *Tetrahedron Lett.* **1983**, *17*, 3009. c) Fronza, G.; Fuganti, C.; Grasselli, P. *Tetrahedron Lett.* **1980**, *21*, 2999. d) Dyong, I.; Bendlin, H.

Chem. Ber. **1979**, *112*, 717. e) Fronza, G.; Fuganti, C; Grasselli, P.; Majori, L.; Pedrocchi-Fantoni, G; Spreafico, F. *J. Org. Chem.* **1982**, *47*, 3289. f) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797. Hirama, M. Shigemoto, T.; Ito, S. *J. Org. Chem.* **1987**, *52*, 3342.

13. a) Saito, S.; Bunya, N.; Inaba, M.; Moriwake, T.; Torri, S. *Tetrahedron Lett.* **1985**, *26*, 5309. b) Dyong, I.; Knolmann, R.; Jersch, N. *Angew. Chem., Int. Edn. Engl.* **1976**, *15*, 302. c) Minami, N. ; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109. d) Danishefsky, S. J; Larson, E. ; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1274. e) Dai, L.; Lou, B;; Zhang, Y. *J. Am. Chem. Soc.* **1988**, *110*, 5195. f) Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.* **1987**, *52*, 5127.
14. Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447.
15. The degree of selectivity was not improved by addition of LiBr and the change of the solvent (methylene dichloride, 1,2-dichloroethane, chloroform, THF, DMF) and base (n-BuLi, THF). Z-selectivity (90 : 10) was observed using the preformed phosphorane **1** in methanol as described.[3] For other significant examples of olefination of **9** see : a) ref. 12b and 13d. b) Katsuki, T. ; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S. ; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373. c) Hanessian, S.; Botta, M. *Tetrahedron Lett.* **1987**, *28*, 1151. d) Trost, B. M.; Seoane, P.; Mignani, S.; Acemoglu, M. *J. Am. Chem. Soc.* **1989**, *111*, 7487. e) Leonard, J.; Ryan, G.; *Tetrahedron Lett.* **1987**, *28*, 2525.
16. Yamamoto, Y. Nishii, S; Ibuka, T. *J. C. S., Chem. Commun.* **1987**, 464.
17. No reaction was observed between benzylamine and the 2-alkenylthiazole **10a** in methanol after 48 hours at room temperature.
18. Because of the various manipulations of the reaction mixture, it is very likely that the actual diastereoselectivity is higher than the quoted value.
19. It is worth pointing out that the stereochemical aspects of the nucleophilic conjugate addition to chiral α, β-unsaturated compounds activated by an electron-withdrawing group, is a rather complex and intriguing matter. Syn- and anti-selectivity may depend upon several factors including : i) the olefin geometry; ii) the nature and position of the asymmetric centre(s); iii) the nature of the activating group; iv) the type of nucleophile. See for instance ref. 15e and 16. See also : Larcheveque, M.; Tamagnau, G.; Petit, Y. *J. C. S., Chem. Commun.* **1989**, 91. Isobe, M. ; Ichigawa, Y.; Funabashi, Y.; Mio, S.; Goto, T. *Tetrahedron* **1986**, *42*, 2863. Lawston, I. W. Inch, T. D. *J. Chem. Soc. Perkin I* **1983**, 2629. Dorigo, A. E.; Morukama, K. *J. Am. Chem. Soc.* **1989**, *111*, 6517.
20. Cherest, M.; Felkin, H. Prudent, N. *Tetrahedron Lett.* **1968**, 2199. Anh, N. T.; Eisenstein, O. *Nouveau J. Chem.* **1977**, *1*, 61. Paddon-Row, M. N. ; Rondan, N. G. Houk, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 7162.
21. Reetz, M. T.; Rohrig, D. *Angew. Chem., Int. Edn. Engl.* **1989**, *28*, 1706.
22. Kirby, J. A. 'The Anomeric Effect and Related Stereoelectronic Effects at Oxygen. Reactivity and Structure Concepts in Organic Chemistry', N. 15, Springer Verlag, Berlin, 1983. Deslongchamps, P. 'Stereoelectronic Effects in Organic Chemistry' Pergamon Press, Oxford, 1983.
23. For an excellent review on the synthesis of these amino sugars, see ref. 10b. For recent papers see ref. 11f and : Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.* **1985**, *107*, 1269. Trost, B. M;

Sudhakar, A. R. *J. Am. Chem. Soc.* **1987**, *109*, 3792. Dai, L.-X; Lou, B.-L.;Zhang, Y.-Z. *J. Am. Chem. Soc.* **1988**, *110*, 5195.

24. Arcamone, F. In 'Anticancer Agents Based on Natural Product Models', Cassay, J. M.; Douros, J. D., Eds.; Academic Press, New York, 1980; Medicinal Chemistry, vol. 16, pp. 1 - 41. See also : Arcamone, F.; Franceschi, G.; Orezzi, P.; Barbieri, W.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5334. Arcamone, F.; Cassinelli, G.; Orezzi, P.; Franceschi, G.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5335.
25. Dyong, I.; Wiemann, R. *Chem. Ber.* **1980**, *113*, 1592.
26. Servi, S. *J. Org. Chem.* **1985**, *50*, 5865.
27. Dyong, I.; Bendlin, H. *Chem. Ber.* **1979**, *112*, 717.
28. For the synthesis of lincosamine see ref. 13d and references cited therein.
29. 'Dictionary of Organic Compounds', Eyre and Spottiswoode, London, 1965, vol. 4, p. 2340.