# Vitamin C and Isovitamin C Derived Chemistry. 2. Synthesis of Some Enantiomerically Pure 4,5,6-Trihydroxylated Norleucines

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A sequence leading to enantiomerically pure 4,5,6-trihydroxylated norleucines **23–25**, their 5,6-*O*-isopropylidene derivatives **17a,b** and **20**, and lactones **19a,b** and **22** from relatively inexpensive carbohydrate precursors is described. 5,6-*O*-Isopropylidene-L-gulono-, -D-mannono-, and -D-galactono-1,4-lactones (**2a,b** and **7b**) react readily with 2 equiv of mesyl chloride in pyridine at 0 °C to produce hex-2-enono-1,4-lactone 2-mesylates **5a,b** and **8**. The butenolides are stereoselectively reduced to 3-deoxyhexono-1,4-lactone 2-mesylates **11a,b** and **12**, which are then treated with sodium azide in DMF to generate the configurationally C-2-inverted azides **15a,b** and **16**. Hydrogenation thereof, in the presence of triethylamine, gives the 5,6-O-isopropylidenated title compounds **17a,b** and **20**, which are hydrolyzed in boiling water to give amino acids **23–25** and are converted into lactones **19a,b** and **22** by treatment with dilute hydrochloric acid under reflux. The lactones are optimally produced directly from **15a,b** and **16** by hydrogenation in the presence of acid.

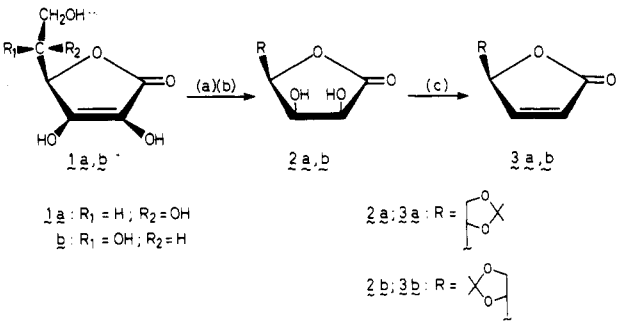
The ascorbic acids **1a,b** represent inexpensive industrially produced bulk chemicals whose potential as a source of chiral carbon compounds has been little exploited.[1] A recent[2] publication describes their transformation into chirally defined butenolides **3a,b** via Hanessian-type dideoxygenations of their reduced 5,6-*O*-isopropylidene acetals **2a,b** (Scheme I). Continuation of these studies required the development of more efficient ways for preparing **3a,b** from **2a,b** in larger quantities. Olefins are known to arise via the reductive elimination of *vic*-ditosylates and -dimesylates[3] (tosyl = *p*-tolylsulfonyl; mesyl = methylsulfonyl). Attention was directed therefore toward converting **2a,b** and subsequently **7b** into **4a,b** and **9c**. Conventional mesylations, however, were found to proceed beyond the production of **4a,b** and **9c**, to give instead, 2-mesylated hex-2-enono-1,4-lactones **5a,b** and **8** cleanly and efficiently. The present report describes some aspects of these reactions, the resultant products, and their subsequent conversion into enantiomerically pure trihydroxylated norleucine analogues **23–25**.

## Results and Discussion

**Mesylation Studies.** Treatment of **2a** in ice-cold pyridine with 2 equiv of mesyl chloride produced a crystalline product in excellent yield. NMR spectroscopy revealed the presence of one mesyl group at 3.3 ppm and a vinylic doublet at 7.15 ppm ($J$ = 2 Hz). In conjunction with analytical data, it was assigned structure **5a**. Examination of the crude product mixtures (NMR; TLC) failed to reveal the presence of **4a**. The comparable reaction of **2a** with 1 equiv of mesyl chloride produced **6a** regioselectively in high yield; its structure was supported by spectral evidence. This showed a doublet ($J$ = 5 Hz) at 5.59 ppm for the proton geminal to the mesylate. Monomesylation of **2a** would be expected to occur preferentially at the C-2 rather than at the C-3 OH in view of the formers' greater acidity and accessibility. Subsequent treatment of **6a** with mesyl chloride in pyridine led to **5a**, most likely through the intermediacy of the dimesylate **4a**.

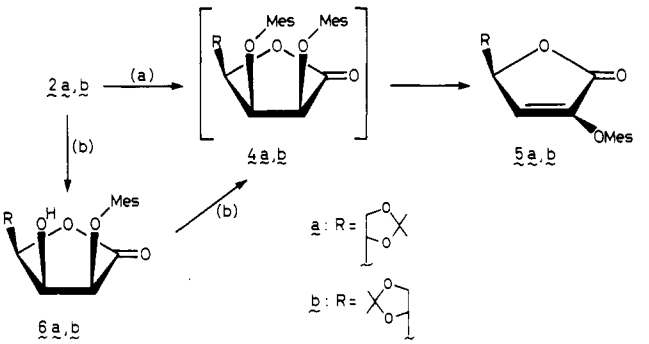
Similar treatment of acetal **2b** with 2 equiv of mesyl chloride proceeded less cleanly to produce 45% of **5b** as the main product. Monomesylate **6b** resulted on treatment of **2b** with 1 equiv of mesyl chloride. No improvement in the overall yield of **5b** was noted when **6b** was allowed to

**Scheme I**[a]




[a] Key: (a) Pd-C, $H_2$; (b) $Me_2C(OMe)_2$, $SnCl_2$; (c) $(MeO)_2CHNMe_2$, reflux $CHCl_3$, azeotropic MeOH removal; MeI/$CH_3CN$/Δ.

**Scheme II**[a]




[a] Key: (a) 2 equiv of MesCl, pyridine, <0 °C; (b) 1 equiv of MesCl, pyridine, <0 °C.

(1) See citations 1–6 in: Vekemans, J. A. J. M.; Boerekamp, J.; Godefroi, E. F.; Chittenden, G. J. F. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 266.

(2) Vekemans, J. A. J. M.; Boerekamp, J.; Godefroi, E. F.; Chittenden, G. J. F. *Recl. Trav. Chim. Pays-Bas* **1985**, *104*, 266.

(3) Block, E. In *Organic Reactions*; Wiley: New York, 1983; Vol. 30, p 499.

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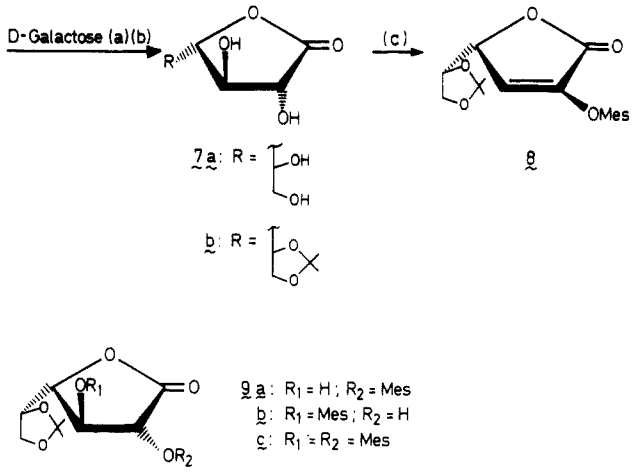
**Scheme III**[a]




[a] Key: (a) Pd–C, aqueous NaOH (pH 9.5), $O_2$; excess acid; (b) $Me_2C(OMe)_2$, $SnCl_2$, dioxane; (c) 2 equiv of MesCl, pyridine, <0 °C.

react with additional mesyl chloride. The butenolide was also obtained by the reaction of **6b** with phosphorus oxychloride in pyridine. Compound **5b** was obtained optimally (55%) by subjecting **2b** in pyridine to the successive action of 1 equiv of mesyl chloride and phosphorus oxychloride in a one-pot sequence (Scheme II).

The L-threo and D-erythro isomers **5a,b** differ spectrally, featuring vinylic doublets at 7.15 vs. 7.29 ppm and H-4 signals at 5.11 vs. 4.88 ppm. Their H-4–H-5 coupling constants amounted to 3.5 and 7 Hz, respectively. Compound **5a** showed broader H-5 and H-6 multiplets and less separation between the methyl signals of the isopropylidene group.

Compounds **5a,b** must clearly have arisen by way of the trans elimination of MesOH from **4a,b**. It was, therefore, of interest to examine the feasibility of exploiting comparable cis eliminations as a way of generating related hex-2-enono-1,4-lactone 2-mesylates. The synthesis of **7b** was therefore undertaken. Molar scale catalytic oxidation of D-galactose (aqueous NaOH, pH 9.5, Pd–C; $O_2$; 55 °C; 0.5 h) provided aqueous solutions of sodium D-galactonate, which on acidification and evaporation yielded D-galactono-1,4-lactone **7a** (60%). (We gratefully acknowledge the technical expertise and supervision of Prof. Dr. K. van der Wiele and Dr. B. F. M. Kuster for the catalytic D-galactose oxidation.)

Compound **7a** was treated[4] with 2,2-dimethoxypropane–dioxane in the presence of tin(II) chloride to give excellent yields of syrupy 5,6-*O*-isopropylidene-D-galactono-1,4-lactone (**7b**). This procedure was considered to be an improved simplification of preexisting methods for preparing **7b**.[5,6]

Acetal **7b** was allowed to react with 2 equiv of mesyl chloride in cooled pyridine to give 50% of a crystalline product characterized as **8**, on the basis of elementary analysis and spectral evidence. Dimesylate **9c** was presumed to be the logical intermediate. Attempts at monomesylating **7a** regioselectively were unsuccessful and gave product mixtures containing small amounts of isolated **8**. These results reflect the greater similarity of the C-2 and C-3 OH groups of **7b** as compared to those of **5a,b**, causing the formation of monoesters **9a** or **b** to be less

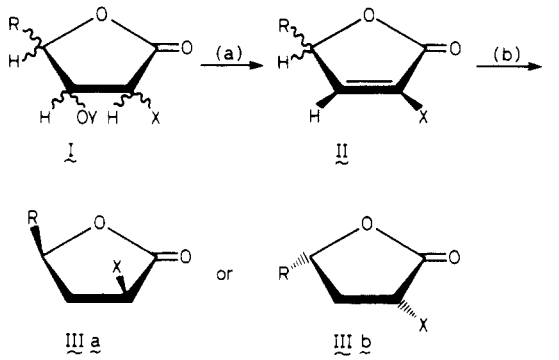
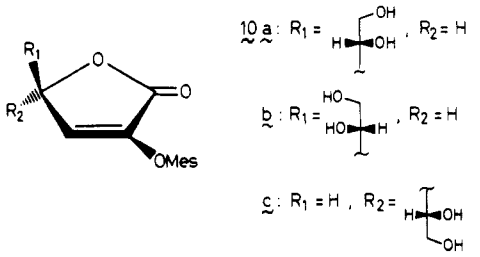



**Figure 1.** I–IIIa,b: R = compatibly functionalized one, two, or three-carbon fragment; Y = Ac, Bn, Bz, Ts; X = NHAc, OAc, OBz, OBn, Br, OTs; (a) -HOY, (b) catalytic reduction.

selective. Cis elimination of the coproduct **9c** would then account for the observed presence of 8 (Scheme III).

Compounds **5a,b** and **8** were further characterized by their conversion to the deprotected diols **10a–c** by acid hydrolysis in propan-2-ol solution.

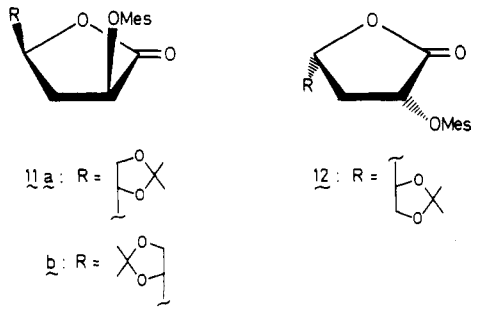



Literature precedents for the base-induced elimination of variously disubstituted aldono-1,4-lactones (type I) to 2-substituted butenolides (type II) have included the preparation of 2-acetamido-,[7] acetoxy-,[8] (benzoyloxy)-,[9] (benzyloxy)-,[10] bromo-,[11] iodo-,[2] and [(*p*-tolylsulfonyl)oxy]-,[12] pent-, hex-, and hept-2-enono-1,4-lactones. In some cases these have been reduced to 3-deoxy lactones IIIa or b[8] which, in other examples, have been obtained directly from I under reductive elimination conditions.[13]

The stereoselectivity of the hydrogenations led, in all cases studied, to the reintroduction of chirality at C-2 and the establishment of a cis relationship between the C-2 and C-4 substituents (Figure 1).

In the present investigation catalytic hydrogenation of **5a** produced stereoselectively 75% of **11a**, whose NMR spectrum (Table I) was consistent with the assigned structure. It featured the following coupling constants: $J_{2,3}$ = 9 Hz, $J_{2,3'}$ = 10.5 Hz, $J_{3,4}$ = 6 Hz, $J_{3',4}$ = 9.5 Hz. Similar data (vide infra) have been reported for related 2-O-substituted 3-deoxy 1,4-lactones.[8a,9a,13–15] Analogous reduc-

(4) Chittenden, G. J. F. *Carbohydr. Res.* **1980**, *87*, 219.
(5) Copeland, C.; Stick, R. V. *Aust. J. Chem.* **1978**, *31*, 1371.
(6) (a) Morgenlie, S. *Acta Chem. Scand. Ser. B* **1975**, *B29*, 367. (b) Morgenlie, S. *Carbohydr. Res.* **1982**, *107*, 137.
(7) (a) Pravdic, N.; Fletcher, H. G., Jr. *Carbohydr. Res.* **1971**, *19*, 339; (b) Zissis, E.; Diehl, H. W.; Fletcher, H. G., Jr. *Carbohydr. Res.* **1973**, *28*, 327.
(8) Attwood, S. V.; Barrett, A. G. M. *J. Chem. Soc., Perkin Trans. 2* **1984**, 315. (b) Barrett, A. G. M.; Sheth, H. G. *J. Chem. Soc., Chem. Commun.* **1982**, 170. (c) Barrett, A. G. M.; Sheth, H. G. *J. Org. Chem.* **1983**, *48*, 5017.
(9) (a) Varela, O. J.; Cirelli, A. F.; De Lederkremer, R. M. *Carbohydr. Res.* **1982**, *100*, 424. (b) Sala, L. F.; Cirelli, A. F.; De Lederkremer, R. M. *Carbohydr. Res.* **1980**, *78*, 61. (c) Litter, M. I.; De Lederkremer, R. M. *Carbohydr. Res.* **1978**, *26*, 431.
(10) Timpe, W.; Dax, K.; Wolf, N.; Weidmann, H. *Carbohydr. Res.* **1975**, *39*, 53.
(11) Pederson, C.; Bock, K.; Lundt, I. *Pure Appl. Chem.* **1978**, *50*, 1385.
(12) Barton, D. H. R.; Benechie, M.; Khuong-Huu, F.; Potier, R.; Reyna-Pinedo, V. *Tetrahedron Lett.* **1982**, *23*, 651.
(13) Bock, K.; Lundt, I.; Pederson, C. *Acta Chem. Scand., Ser. B* **1981**, *B35*, 155.
(14) De Lederkremer, R. M.; Litter, M. I. *Carbohydr. Res.* **1971**, *20*, 442.

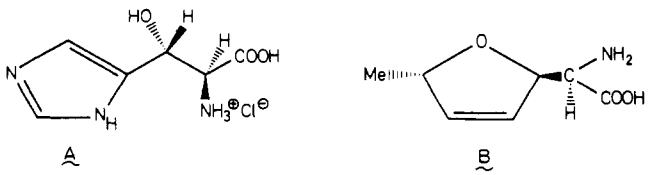



tions transformed **5b** and **8** into **11b** and **12**. NMR spectroscopy showed $\sum J_{3,4} + J_{3',4} \sim 16$ Hz. The isopropylidene methyl group signals were spaced further apart in the D-arabino compound **11b** than in the corresponding L-xylo derivative **11a** (Table I). Compounds **5a** and **8** and also their reduction products **11a** and **12** constitute enantiomeric pairs.

The modes of formation of **5a,b** and **8** from **4a,b** and **9c** merit additional comment. Whereas **5a,b** must have ensued from the trans elimination of methanesulfonic acid from **4a,b**, the generation of **8** via an apparent cis elimination from **9c** is less evident. We suggested recently that the cis elimination of formate ester intermediate **13** to **14** may have involved a six-center transition state promoted by the carbonyl- and iodo-enhanced acidity of H(2)[2] (Scheme IV).

An $E_1$ mechanism had been proposed earlier for a related cis elimination.[9c] The possibility of **7b** having undergone C-2 epimerization prior to elimination was considered unlikely since NMR-monitored control experiments demonstrated the monomesylates **6a,b**, **11a,b**, and **12** to be resistant toward pyridine-induced deprotonation at C-2. These results, however, did not rule out the possibility of pyridine eliciting the deprotonation and consequential enolization of dimesylates **4a,b** and **9c**, thus leading to intermediates IVa,b and V. The subsequent expulsion of the C-3 mesylate would then give **5a,b** and **8** (Scheme V). Such an $E_{1c,b}$ mechanism would obviate the need of invoking cis and trans elimination pathways and would reduce the issue to one of minor differences in the kinetic acidity of the proton on C-2. The process would derive its impetus from the relief of nonbonded interactions between substituents at C-2, C-3, and C-4 and would be accelerated sterically (Scheme V).

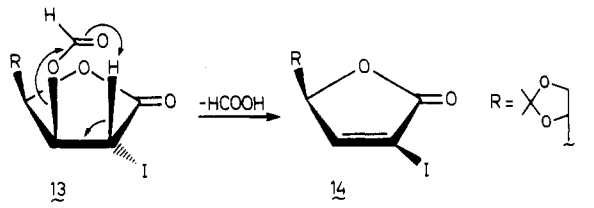
The synthetic potential of **5a,b** and **8** differs fundamentally from that of their congeners depicted in Figure 1. Whereas all the stereocontrolled reductions had given rise to products featuring their C-2 and C-4 substituents in a cis relationship, the nucleophilic displacement of the C-2 mesylate fragments encountered in reduction products **11a,b** and **12** would lead to structures having their substituents in a trans geometry. To test the concept in a scheme for constructing D- or L-amino acid derivatives, the preparation of enantiomerically pure 4,5,6-trihydroxylated norleucines **23–25** was undertaken. Carbohydrates have previously been applied in the elaboration of chiral $\alpha$-amino acids such as the bleomycin component L-erythro-$\beta$-hydroxyhistidine[16] (**A**) and (+)-furanomycin[17] (**B**).



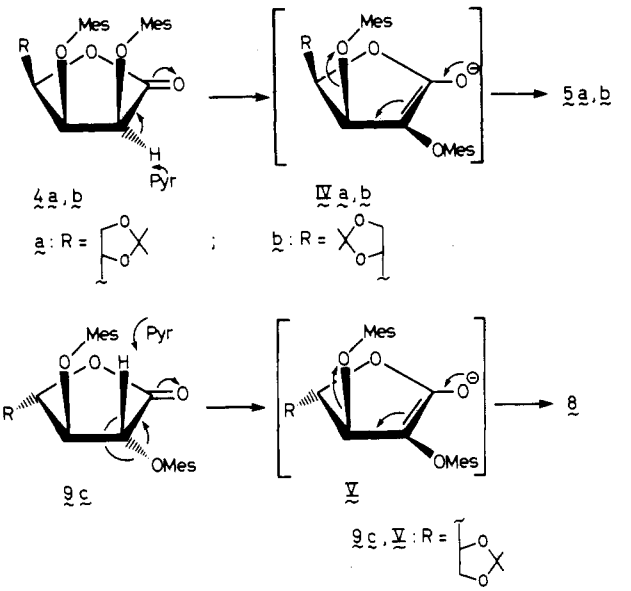
**A** **B**

(15) (a) Chmielewski, M. *Tetrahedron* **1980**, *36*, 2345. (b) Unpublished data from these laboratories.

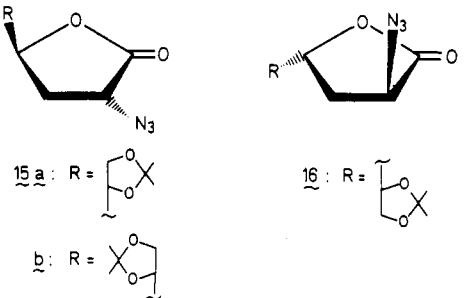
**Scheme IV**




**Scheme V**



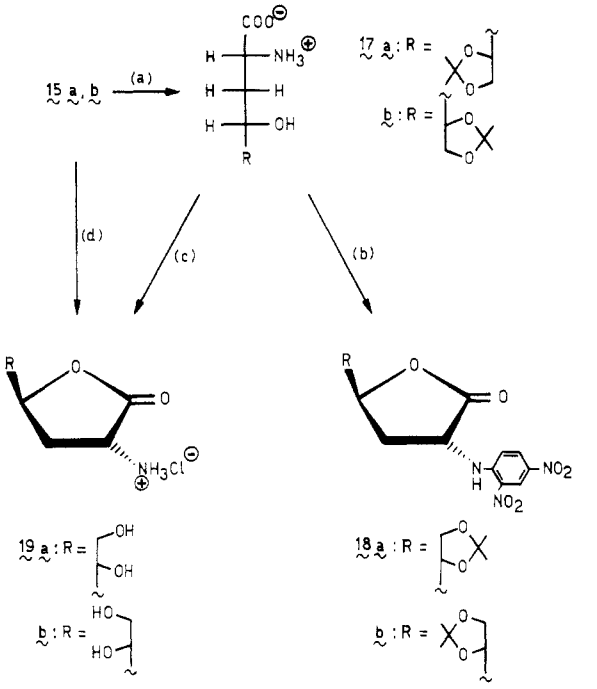

**Synthesis of 23–25.** Compound **11a** was treated therefore with sodium azide in DMF at room temperature to give 90% of the pure azido derivative **15a**. Its structural assignment was based on the earlier described elucidation of the geometry of 3-deoxy 2,4-disubstituted 1,4-lactones.[18] These studies had shown the sum of the ring proton vicinal coupling constants to be greater for the cis isomers than for their trans counterparts. The differences have been ascribed to the change of an axial–axial interaction to an equatorial–equatorial one on going from the cis to the trans isomers. Compound **15a** revealed $\sum J_{3,4} + J_{3',4} = 12.5$ Hz being in agreement with its proposed C-2–C-4 trans geometry. Similar azide displacements on mesylates **11b** and **12** led to the NMR-supported structures **15b** and **16**. In contrast with **15a** and **16**, the methyl signals of the isopropylidene group of **15b** showed a clearly defined separation (Table I).




Catalytic reduction (10% Pd–C, 1 equiv of triethylamine, 75% EtOH, 50 lbs/in.$^2$) of **15a** yielded 86% of solid

(16) Hecht, S. M.; Rupprecht, K. M.; Jacobs, P. M. *J. Am. Chem. Soc.* **1979**, *101*, 3982.
(17) Joullié, M. M.; Wang, P. C.; Semple, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 887.
(18) Hussain, S. A. M. T.; Ollis, W. D.; Smith, C.; Stoddart, J. F. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1480.

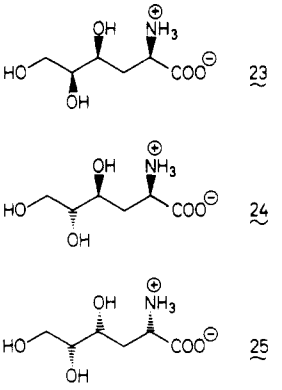
**Scheme VI**[a]



[a] Key: (a) $H_2$, Pd–C, aqueous EtOH, $Et_3N$; (b) 2,4-dinitro-1-fluorobenzene, DMF, $K_2CO_3$; (c) aqueous HCl; (d) $H_2$, Pd–C, aqueous EtOH, HCl.

material. The broad IR absorption maxima at 3500–2500 and 1600 $cm^{-1}$ characterized the product as an amino acid zwitterion. In conjunction with NMR data, showing the presence of an isopropylidene group, it was assigned structure **17a**. The retention of the original configuration at C-2 was substantiated by the NMR spectrum of the (2,4-dinitrophenyl)amino compound **18a**. This was obtained by treatment of **17a** with 2,4-dinitrofluorobenzene–$K_2CO_3$ in DMF and subsequent acidification with oxalic acid to give a mixture of mono- and disubstituted derivatives. The chromatographically pure, mono-N-substituted product **18a** was crystallized from methanol. Its NMR spectrum was rather complex due to the additional NH–CH coupling. The H-3 and H-3′ absorption pattern is also influenced strongly by the solvent used: in $CDCl_3$ a 16-peak multiplet was observed, as in all other 3-deoxy 2,4-disubstituted 1,4-lactones studied, but in $Me_2SO$-$d_6$ both protons coincided to simplify the signal to that of a doublet of doublets ($J_{2,3}$ = 9.5 Hz, $J_{3,4}$ = 6 Hz). These data suggest a 2,4-trans geometry for the substituents on **18a** and hence also for the ones on **17a**. The amino acid **17a** gave the corresponding deprotected 1,4-lactone **19a** on treatment with aqueous HCl. The product was characterized spectroscopically, showing γ-lactone absorption at 1800 $cm^{-1}$ (infrared) and the absence of an isopropylidene acetal fragment (NMR). Catalytic reductions of **15b** and **16** in the manner described for **15a** yielded amino acids **17b** and **20**, which were characterized as the (2,4-dinitrophenyl)amino analogues **18b** and **21**. They also underwent acid-catalyzed deprotection and lactonization to give **19b** and **22**. Lactones **19a,b** and **22** were best obtained directly from **15a,b** and **16** by catalytic hydrogenation under acidic conditions (Scheme VI).

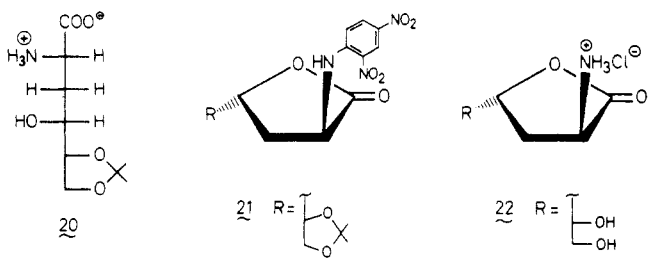
The action of boiling water transformed partially protected **17a,b** and **20** into the free amino acids **23–25**. Since



these were difficult to handle, they were derivatized and purified as their copper(II) salts. Compound **19b** has been reported[19] previously in a sequence for the preparation of the antipode of naturally occurring muscarine through the assumed intermediacy of structure **24**.

## Concluding Remarks

Compounds **23–25** may be viewed as 4,5,6-trihydroxylated norleucines or as 3-deoxyhexosaminic acids; formally they represent terminally $sp^3$-carbon-linked alanine and glycerol units. Hexosaminic acids have been obtained by way of the C-1 oxidation of aldosamines[19] and by the Strecker homologation of the lower aldoses.[21] 2-Acetamido-2-deoxy-D-mannono-1,4-lactone has been obtained by way of the C-2 epimerization of D-glucosaminic acid.[16] Of the 3-deoxyhexosaminic acids, only **24** has been reported previously via a non-carbohydrate approach.[19] The present route for preparing **23–25** exploits aldono-1,4-lactone chemistry throughout. Whereas carbohydrate-based schemes for constructing chiral carbon compounds have almost invariably been predicated on furanoside and pyranoside transformations,[22] concepts centering on aldono-1,4-lactones have attracted surprisingly little attention. Their potential in synthesis stems from the following. Aldono-1,4-lactones and their lactols constitute interconvertible synthetic equivalents. Generous amounts of starting lactones can be prepared by the catalytic oxidation of the corresponding aldoses; L-gulono- and D-mannono-1,4-lactones are obtained from the Pd-catalyzed reduction of the plentiful ascorbic acids **1a,b**.[2] The presence at C-1 of a carbonyl group rather than a conventional anomeric center contributes to the ring stability under a range of conditions, while promoting deprotonation and nucleophilic displacement reactions at C-2. The conformational stability of the γ-lactone rings makes them



(19) Hardegger, E.; Furter, H.; Kiss, J. *Helv. Chim. Acta* **1958**, 41, 2405.

(20) (a) Hardegger, E.; Lohse, F. *Helv. Chim. Acta* **1957**, *40*, 2383. (b) Wolfrom, M. C.; Cron, M. J. *J. Am. Chem. Soc.* **1952**, 74, 1715. (c) Pringsheim, H.; Rushmann, G. *Ber.* **1965**, *48*, 680.

(21) Kuhn, R.; Kirshenlohr, W. *Justus Liebigs Ann. Chem.* **1965**, *600*, 115.

(22) Carbohydrate-based schemes for synthesizing chiral carbon compounds have been reviewed: (a) Fraser-Reid, B. *Acc. Chem. Res.* **1975**, *8*, 192. (b) Fraser-Reid, B.; Anderson, R. C. *Prog. Chem. Org. Nat. Prod.* **1980**, *39*, 1. (c) Vasella, A. In *Modern Synthetic Methods*; Otto Sella Verlag: Frankfurt am Main, Germany, 1980; p 173. (d) Hanessian, S. *Total Synthesis of Natural Products: The Chiron Approach*; Pergamon: Oxford, 1983.

**Table I. Relevant $^1$H NMR Data of 2,4-Disubstituted γ-Lactones[a]**

| | R-2 | R-4 | config | δ(H-2) | Δδ(H-3–H-3′) | δ(H-4) | Δδ (acetonide Me) | $J_{2,3}$ | $J_{2,3'}$ | $J_{3,4}$ | $J_{3',4}$ | ΣJ | ref |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| cis | *t*-Bu | *t*-Bu | DL | 2.45 | 0.26 | 3.94 | | 8.5 | 12.8 | 6.0 | 10.8 | 38.1 | 18 |
| cis | Ph | Ph | DL | 4.01 | 0.68 | 5.52 | | 8.1 | 12.9 | 5.7 | 10.8 | 37.6 | 18 |
| trans | *t*-Bu | *t*-Bu | DL | 2.37 | 0.04 | 4.06 | | 8.0 | 9.0 | 7.5 | 7.0 | 31.5 | 18 |
| trans | Ph | Ph | DL | 3.92 | 0.13 | 5.65 | | 8.1 | 9.7 | 7.8 | 5.8 | 31.4 | 18 |
| cis | OCOPh | Et | DL | 5.66 | 0.82 | 4.41 | | 8.5 | 10.4 | 6.2 | 10.1 | 35.2 | 9a |
| cis | OCOPh | CH(OCOPh)Me | L-arabino | 5.68 | 0.62 | 4.63 | | 8.4 | 10.2 | 6.5 | 10.0 | 35.1 | 9a |
| cis | OCOPh | $\overline{\text{CHOCMe}_2\text{OCH}_2}$ | L-xylo | 5.69 | 0.46 | 4.50 | 0.06 | 9 | 10 | 6 | 10 | 35 | 15b |
| trans | OCOPh | $\overline{\text{CHOCMe}_2\text{OCH}_2}$ | L-lyxo | 5.74 | 0.28 | 4.63 | 0.00 | 9 | 9 | 9 | 3 | 30 | 15b |
| cis | OAc | $\text{CH}_2\text{OAc}$ | D-threo | 5.50 | 0.77 | 4.66 | | 8.7 | 10.2 | 6.2 | 9.8 | 34.9 | 13 |
| | | | | 5.54 | 0.67 | 4.72 | | 8.8 | 10.3 | 5.9 | 10.3 | 35.3 | 8a |
| cis | OAc | CHOAcMe | D-xylo | 5.51 | 0.73 | 4.47 | | 8.8 | 10.5 | 5.5 | 10.4 | 35.2 | 13 |
| | | | DL-xylo | 5.50 | | 4.51 | | 8.7 | 10.5 | 6.0 | 9.8 | 35.0 | 15a[b] |
| | | | DL-arabino | 5.48 | | 4.48 | | 8.6 | 10.2 | 6.0 | 9.4 | 34.2 | 15a |
| cis | OAc | $\text{CHOAcCH}_2\text{OAc}$ | D-xylo | 5.31 | 0.57 | 4.51 | | 9.0 | 10.5 | 6.0 | 9.0 | 34.5 | 13 |
| | | | DL-xylo | 5.48 | | 4.70 | | 8.7 | 10.3 | 5.7 | 9.5 | 34.2 | 15a |
| | | | DL-arabino | 5.47 | | 4.66 | | 8.5 | 10.1 | 6.0 | 9.7 | 34.3 | 15a |
| trans | OAc | CHOAcMe | DL-lyxo | 5.38 | | 4.66 | | 8.0 | 9.0 | 7.3 | 3.9 | 28.2 | 15a |
| | | | DL-ribo | 5.42 | 0.33 | 4.62 | | 7.7 | 9.0 | 9.3 | 3.2 | 29.2 | 15a |
| trans | OAc | $\text{CHOAcCH}_2\text{OAc}$ | DL-lyxo | 5.35 | | 4.85 | | 8.0 | 9.0 | 7.6 | 4.5 | 29.1 | 15a |
| | | | DL-ribo | 5.39 | 0.32 | 4.82 | | 7.5 | 9.0 | 8.1 | 3.7 | 29.3 | 15a |
| cis | I | $\overline{\text{CHOCMe}_2\text{OCH}_2}$ | L-xylo | 4.70 | 0.39 | | 0.05 | 9 | 9.5 | 7 | 7 | 32.5 | 15b |
| trans | I | $\overline{\text{CHOCMe}_2\text{OCH}_2}$ | L-lyxo | 4.64 | 0.19 | | 0.00 | 7 | 4.5 | 6 | 7 | 24.5 | 15b |
| cis[c] | OMes | $\overline{\text{CHOCMe}_2\text{OCH}_2}$ | L-xylo | 5.50 | 0.56 | 4.61 | 0.04 | 9 | 10.5 | 6 | 9.5 | 35 | **11a** |
| | | | D-xylo | 5.55 | 0.56 | 4.63 | 0.04 | 9 | 10.5 | 6 | 9.5 | 35 | **12** |
| | | | D-arabino | 5.59 | 0.54 | 4.57 | 0.08 | 9 | 10 | 5.5 | 9.5 | 34 | **11b** |
| trans | $N_3$ | $\overline{\text{CHOCMe}_2\text{OCH}_2}$ | L-lyxo | 4.51 | 0.34 | 4.55 | 0.00 | 9.5 | 8.5 | 9.5 | 3 | 30 | **15a** |
| | | | D-lyxo | 4.50 | 0.33 | 4.54 | 0.00 | 9.5 | 8.5 | 9.5 | 3 | 30 | **16** |
| | | | D-ribo | 4.39 | 0.34 | 4.48 | 0.13 | 8.5 | 8.5 | 8.5 | 3.5 | 29 | **15b** |
| trans[d] | NH-2,4-DNP | $\overline{\text{CHOCMe}_2\text{OCH}_2}$ | L-lyxo | 4.97 | 0.0 | | 0.00 | 9.5 | 9.5 | 6 | 6 | 31 | **18a** |
| | | | D-lyxo | 4.98 | 0.0 | | 0.00 | 9.5 | 9.5 | 6 | 6 | 31 | **21** |
| | | | D-ribo | 5.04 | 0.0 | | 0.11 | 9.5 | 9.5 | 6 | 6 | 31 | **18b** |
| trans[e] | $NH_3^+Cl^-$ | $\text{CHOHCH}_2\text{OH}$ | L-lyxo | 4.65 | 0.11 | 5.09 | | 10.5 | 9 | 8 | 3.5 | 31 | **19a** |
| | | | D-ribo | 4.62 | 0.26 | 5.34 | | 10.5 | 9 | 8 | 2.5 | 31 | **19b** |

[a] Unless otherwise stated, $CDCl_3$ was used as solvent; δ values; *J* values, hertz. H-3 refers to the proton trans; H-3′, to the proton cis with respect to R-4. [b] It is recognized that the published cis–trans assignments must be reversed. [c] In acetone-$d_6$. [d] In $Me_2SO$-$d_6$. [e] In $D_2O$.

attractive substrates for the restructuring of monosaccharides by way of relatively straightforward processes. In practice, aldono-1,4-lactones are highly crystalline and easily manipulated substances, readily identified by NMR spectroscopy. These aspects are borne out by the aldono-1,4-lactone-based syntheses of **23–25** via easily handled solid lactone intermediates derived from inexpensive bulk chemicals. The concept is an efficient one in giving access to both D- and L-amino acid derivatives whose C-2 stereochemistry is laid down by the original C-4 configuration of the unsaturated mesylates **5a,b** and **8**. Reduction of (4*S*,5*S*)-**5a** and (4*S*,5*R*)-**5b** produces (2*S*,4*S*,5*S*)- and (2*S*,4*S*,5*R*)-**11a,b** and ultimately the D-amino acids (2*R*,4*S*,5*S*)-**23** and (2*R*,4*S*,5*R*)-**24**. The L-amino acid (2*S*,4*R*,5*R*)-**25** originates via the parallel elaboration of reduction product (2*R*,4*R*,5*R*)-**12** obtained from (4*R*,5*R*)-**8**.

## Experimental Section

**General Methods.** Microanalytical data were supplied by H. Eding. Proton NMR spectra were recorded on a Hitachi Perkin-Elmer R24B spectrometer, $Me_4Si$ as internal standard. Optical rotations were determined on an optical activity AA-10 polarimeter. Melting points (recorded on a Fischer-Johns block) are uncorrected. Column chromatography was carried out on silica gel (Merck, Kieselgel 60) and thin-layer chromatography (TLC) on aluminum sheets precoated with silica gel (Merck, Art. 5554).

**3-Deoxy-5,6-*O*-isopropylidene-2-*O*-mesyl-L-*threo*-hex-2-enono-1,4-lactone (5a).** Mesyl chloride (26.4 g, 0.23 mol) was added dropwise over 0.5 h to a cooled (−10 °C), stirred solution of 5,6-*O*-isopropylidene-L-gulono-1,4-lactone[2] (**2a**; 21.8 g, 0.10 mol) in pyridine (64 mL). The reaction was allowed to proceed for a further 5 h at 0 °C wherein ice–water (300 mL) was added and the mixture stirred at room temperature for 0.5 h. The precipitated crude product was collected by filtration, washed successively with water (300 mL), methanol (75 mL), and ether (50 mL), and recrystallized from methanol to yield title product **5a**: 22.5 g (81%); mp 121–122 °C; $[\alpha]^{20}_D$ −41° (*c* 1.81, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.38 (s, 3 H), 3.34 (s, 3 H), 3.6–4.6 (m, 3 H), 5.10 (dd, *J* = 3.5 and 1.75 Hz, 1 H), 7.14 (d, *J* = 1.75 Hz, 1 H). Anal. Calcd for $C_{10}H_{14}O_7S$: C, 43.16; H, 5.07. Found: C, 43.3; H, 5.2.

**5,6-*O*-Isopropylidene-2-*O*-mesyl-L-gulono-1,4-lactone (6a).** Mesyl chloride (2.29 g, 0.02 mol) was added dropwise over 0.5 h to a stirred, cooled (−10 °C) solution of acetal **2a** (4.3 g, 0.02 mol) in pyridine (10 mL), maintaining the temperature below −5 °C. The reaction was then allowed to proceed at 0 °C for 1 h, after which water (80 mL) was added. The precipitated crude product was collected by filtration, washed successively with water, propan-2-ol, and ether, and then triturated with propan-2-ol to give compound **6a**: 4.25 g (76%); mp 182–184 °C; $[\alpha]^{20}_D$ +18.5° (*c* 0.92, $CHCl_3$); $^1$H NMR (deuterioacetone) δ 1.34 (s, 3 H), 1.38 (s, 3 H), 3.29 (s, 3 H), 4.3–4.7 (m, 6 H), 5.59 (d, *J* = 4.5 Hz, 1 H). Anal. Calcd for $C_{10}H_{16}O_8S$: C, 40.54; H, 5.44. Found: C, 40.5; H, 5.4.

**3-Deoxy-5,6-*O*-isopropylidene-2-*O*-mesyl-D-*erythro*-hex-2-enono-1,4-lactone (5b).** Mesyl chloride (7.22 g, 0.063 mol) was added dropwise over 15 min to a stirred, cooled (−10 °C) solution of 5,6-*O*-isopropylidene-D-mannono-1,4-lactone[2] (**2b**; 12.0 g, 0.055 mol) in pyridine (35 mL) and the resultant mixture allowed to proceed at 0 °C for 1.25 h. The mixture was then recooled to −10 °C, treated dropwise over 15 minutes with phosphorus oxychloride (9.63 g, 0.063 mol), and then allowed to proceed at 0 °C for 3 h. Ice–water (165 mL) was added to the mixture, and after being kept at room temperature for 0.5 h the crude product was collected by filtration and washed successively with water (165 mL),

methanol (55 mL), and ether (35 mL). Recrystallization of this material [9.43 g (62%)] from methanol gave title product **5b**: 8.37 g (55%); mp 109–110 °C; $[\alpha]^{20}_D$ –86° (*c* 1.76, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.44 (s, 3 H), 3.37 (s, 3 H), 3.8–4.2 (m, 3 H), 4.88 (dd, *J* = 6.5 and 1.75 Hz, 1 H), 7.29 (d, *J* = 1.75 Hz, 1 H). Anal. Calcd for $C_{10}H_{14}O_7S$: C, 43.16; H, 5.07. Found: C, 43.2; H, 5.2.

**5,6-*O*-Isopropylidene-2-*O*-mesyl-D-mannono-1,4-lactone (6b).** Treatment of compound **2b** (1 equiv) with mesyl chloride (1 equiv) in the same manner as described for the acetal **2a** gave compound **6b** (66%) after recrystallization from propan-2-ol: mp 150–151 °C; $[\alpha]^{20}_D$ +17.5° (*c* 1.70, $CHCl_3$); $^1H$ NMR (deuterioacetone) δ 1.34 (s, 3 H), 1.42 (s, 3 H), 2.7 (s, 1 H), 3.28 (s, 3 H), 4.0–4.9 (m, 5 H), 5.48 (d, *J* = 4.5 Hz, 1 H). Anal. Calcd for $C_{10}H_{16}O_8S$: C, 40.54; H, 5.44. Found: C, 41.1; H, 5.6.

**5,6-*O*-Isopropylidene-D-galactono-1,4-lactone (7b).** A stirred suspension of lactone **7a** (53.4 g, 0.3 mol) in boiling 1,4-dioxane (300 mL) and 2,2-dimethoxypropane (46.5 mL) was treated with anhydrous stannous chloride (100 mg) and the mixture heated under reflux for 0.25 h. The cooled mixture was treated with pyridine (1 mL) and concentrated in vacuo. The resulting syrup was dissolved in dichloromethane–acetone (2:1, 500 mL) and filtered through silica gel (200 g), which was then eluted further with dichloromethane–acetone (1:1, 500 mL). The combined filtrate and eluate was concentrated in vacuo to product **7b**, as a pale yellow syrup: 61.6 g (94%); $[\alpha]^{20}_D$ –42° (*c* 2.01, acetone) [lit.[5] –46°; lit.[6a] –42°]; $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.33 (s, 6 H), 3.8–4.3 (m, 6 H), 5.88 (d, *J* = 5.5 Hz, 1 H), 6.03 (d, *J* = 6 Hz, 1 H).

**3-Deoxy-5,6-*O*-isopropylidene-2-*O*-mesyl-D-*threo*-hex-2-enono-1,4-lactone (8).** Treatment of a cooled, stirred solution of acetal **7b** (21.8 g, 0.10 mol) with mesyl chloride (26.4 g, 0.23 mol) in the same manner as described for compound **2a** gave, after recrystallization of the crude product [15.3 g (55%)] from methanol, pure **8**: 13.8 g (50%); mp 121–122 °C; $[\alpha]^{20}_D$ +42° (*c* 0.58, $CHCl_3$); $^1H$ NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.39 (s, 3 H), 3.35 (s, 3 H), 3.6–4.6 (m, 3 H), 5.11 (dd, *J* = 3.5 and 1.75 Hz, 1 H), 7.15 (d, *J* = 1.75 Hz, 1 H). Anal. Calcd for $C_{10}H_{14}O_7S$: C, 43.16; H, 5.07. Found: C, 43.0; H, 4.8.

**3-Deoxy-2-*O*-mesyl-L-*threo*-hex-2-enono-1,4-lactone (10a).** A suspension of mesylate **5a** (2.78 g, 0.01 mol) in a mixture of propan-2-ol (36 mL) and concentrated HCl (1.5 mL) was heated under reflux, with stirring for 1 h. Concentration of the mixture in vacuo and trituration of the solid residue with dichloromethane (10 mL) gave compound **10a**: 2.21 g (93%); mp 109–110 °C. An analytical sample was obtained by recyrstallizion of a portion of this material from propan-2-ol: mp 109.5–110.5 °C; $[\alpha]^{20}_D$ –16° (*c* 1.82, $H_2O$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 3.50 (s, 3 H), 3.2–3.8 (m, 3 H), 4.9 (s, 2 H), 5.24 (dd, *J* = 3 and 1.5 Hz, 1 H), 7.48 (d, *J* = 1.5 Hz, 1 H). Anal. Calcd for $C_7H_{10}O_7S$: C, 35.30; H, 4.23. Found: C, 35.2; H, 4.2.

**3-Deoxy-2-*O*-mesyl-D-*erythro*-hex-2-enono-1,4-lactone (10b).** Treatment of mesylate **5b** (2.78 g, 0.01 mol) in the manner described above afforded compound **10b** [2.04 g (86%)], an analytical sample of which was obtained by recrystallization from ethyl acetate: mp 94–96 °C; $[\alpha]^{20}_D$ –62° (*c* 1.89, $H_2O$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 3.45 (s, 3 H), 3.3–3.9 (m, 3 H) 4.7 (s, 2 H), 5.19 (dd, *J* = 4 and 1.5 Hz, 1 H), 7.44 (d, *J* = 1.5 Hz, 1 H). Anal. Calcd for $C_7H_{10}O_7S$: C, 35.30; H, 4.23. Found: C, 35.4; H, 3.9.

**3-Deoxy-2-*O*-mesyl-D-*threo*-hex-2-enono-1,4-lactone (10c).** Compound **10c** was prepared as described for **10a** in 94% yield: mp 109–111 °C; $[\alpha]^{20}_D$ +16° (*c* 1.78, $H_2O$); $^1H$ NMR ($Me_2SO$-$d_6$) δ 3.44 (s, 3 H), 3.4–3.9 (m, 3 H), 4.1 (s, 2 H), 5.21 (dd, *J* = 4 and 1.5 Hz, 1 H), 7.49 (d, *J* = 1.5 Hz, 1 H). Anal. Found: C, 35.6; H, 4.1.

**3-Deoxy-5,6-*O*-isopropylidene-2-*O*-mesyl-L-*xylo*-hexono-1,4-lactone (11a).** A mixture of the unsaturated mesylate **5a** (27.8 g, 0.10 mol) and palladized charcoal (10%, 2.0 g), suspended in a mixture of ethyl acetate–water (199:1, 800 mL), was hydrogenated at 50 psi in a Parr apparatus. After 2.5 h the theoretical volume of hydrogen (2.5 L, 1 atm) had been consumed, and the catalyst was removed by filtration and washed well with acetone. The combined filtrate and washings were treated with pyridine (0.4 mL) and concentrated to dryness in vacuo, below 40 °C. Trituration of the residue (28.1 g) with methanol (70 mL) gave pure lactone **11a**: 22.7 g (81%); mp 114–115 °C; $[\alpha]^{20}_D$ –9° (*c* 1.59, $CHCl_3$); $^1H$ NMR (deuterioacetone) δ 1.31 (s, 3 H), 1.35 (s, 3 H), 2.30 (dt, *J* = 12 and 10 Hz, 1 H), 2.86 (ddd, *J* = 6, 9, and 12 Hz, 1 H), 3.25 (s, 3 H), 3.7–4.4 (m, 3 H), 4.61 (ddd, *J* = 4, 6, and 9.5 Hz, 1 H), 5.50 (dd, *J* = 9 and 10.5 Hz, 1 H). Anal. Calcd for $C_{10}H_{16}O_7S$: C, 42.85; H, 5.75. Found: C, 42.9; H, 5.7.

**3-Deoxy-5,6-*O*-isopropylidene-2-*O*-mesyl-D-*arabino*-hexono-1,4-lactone (11b).** Hydrogenation (5 h) of the unsaturated mesylate **5b** (6.22 g, 0.022 mol), in the presence of palladized charcoal (10%, 0.3 g), in the same manner as described above, followed by trituration of the crude product (6.25 g, 100%) with methanol (20 mL) at 0 °C for 1 h gave pure **11b**: 5.10 g (82%); mp 142–143.5 °C; $[\alpha]^{20}_D$ –23° (*c* 0.86, $CHCl_3$); $^1H$ NMR (deuterioacetone) δ 1.32 (s, 3 H), 1.40 (s, 3 H), 2.29 (dt, *J* = 12.5 and 9.75 Hz, 1 H), 2.83 (ddd, *J* = 5.5, 9, and 12.5 Hz, 1 H), 3.33 (s, 3 H), 3.7–4.4 (m, 3 H), 4.57 (dt, *J* = 9.5 and 5.5 Hz, 1 H), 5.59 (dd, *J* = 9 and 10 Hz, 1 H). Anal. Calcd for $C_{10}H_{16}O_7S$: C, 42.85; H, 5.75. Found: C, 42.7; H, 5.8.

**3-Deoxy-5,6-*O*-isopropylidene-2-*O*-mesyl-D-*xylo*-hexono-1,4-lactone (12).** Compound **12** was prepared as described for **11a** in 75% yield: mp 113–114 °C; $[\alpha]^{20}_D$ +9° (*c* 1.62, $CHCl_3$); $^1H$ NMR (deuterioacetone) δ 1.32 (s, 3 H), 1.36 (s, 3 H), 2.30 (dt, *J* = 12 and 10 Hz, 1 H), 2.86 (ddd, *J* = 12, 9, and 6 Hz, 1 H), 3.25 (s, 3 H), 3.8–4.4 (m, 3 H), 4.63 (ddd, *J* = 9.5, 6, and 4 Hz, 1 H), 5.55 (dd, *J* = 10.5 and 9 Hz, 1 H). Anal. Found: C, 43.3, H, 5.7.

**2-Azido-2,3-dideoxy-5,6-*O*-isopropylidene-L-*lyxo*-hexono-1,4-lactone (15a).** A solution of saturated mesylate **11a** (2.80 g, 0.01 mol) in DMF (10 mL) was treated with sodium azide (10 g, 0.015 mol) and allowed to stir at room temperature for 18 h. The mixture was treated with ether (50 mL) and then extracted with water (1 × 20; 5 × 10 mL). The washed, dried ($MgSO_4$) ethereal layer was evaporated in vacuo to give an oil that crystallized on standing. Trituration of the crude product [2.08 g (91%)] with ice-cold diisopropyl ether (4 mL) gave pure azide **15a**: 1.75 g (77%); mp 62–63.5 °C; $[\alpha]^{20}_D$ +198° (*c* 0.97, MeOH); $^1H$ NMR ($CDCl_3$) δ 1.35 (s, 6 H), 2.22 (dt, *J* = 13.5 and 9.5 Hz, 1 H), 2.56 (ddd, *J* =13.5, 8.5, and 3 Hz, 1 H), 3.94 (dd, *J* = 8.5 and 7 Hz, 1 H), 4.07 (dd, *J* = 8.5 and 7 Hz, 1 H), 4.16 (td, *J* = 7 and 2 Hz, 1 H), 4.51 (dd, *J* = 9.5 and 8.5 Hz, 1 H), 4.55 (ddd, *J* = 9.5, 3, and 2 Hz, 1 H); IR (KBr) $\nu_{max}$ 2100 ($N_3$), 1790 $cm^{-1}$ (C=O). Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.9; H, 5.75; N, 18.4.

Azide **15a** was also obtainable (63% yield) from compound **5a** in a one-pot sequence, without prior isolation of intermediate **11a** (vide infra).

**2-Azido-2,3-dideoxy-5,6-*O*-isopropylidene-D-*ribo*-hexono-1,4-lactone (15b).** Treatment of mesylate **11b** in the same way as described for **11a** gave azide **15b**: 4.17 g (73%); mp 60–61.5 °C; $[\alpha]^{20}_D$ +134° (*c* 1.06, MeOH); $^1$NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.45 (s, 3 H), 2.17 (dt, *J* = 13.5 and 8.5 Hz, 1 H), 2.51 (ddd, *J* = 3.5, 8.5, and 13.5 Hz, 1 H), 3.73 (dd, *J* = 8.5 and 5.5 Hz, 1 H), 4.11 (dd, *J* = 8.5 and 7.5 Hz, 1 H), 4.26 (ddd, *J* = 7.5, 5.5, and 4 Hz, 1 H), 4.39 (t, *J* = 8.5 Hz, 1 H), 4.48 (ddd, *J* = 8.5, 4, and 3.5 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 24.4 ($CH_3$), 26.2 ($CH_3$), 29.2 (C-3), 56.4 (C-2), 65.7 (C-6), 75.7 (C-4), 78.0 (C-5), 110.4 ($CMe_2$), 173.05 (C-1); IR (KBr) $\nu_{max}$ 2100 ($N_3$), 1790 $cm^{-1}$ (C=O). Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.8; H, 6.0; N, 18.4.

Azide **15b** was also obtainable (72% yield) from **5b**, without isolation of intermediate compound **11b** (vide infra).

**2-Azido-2,3-dideoxy-5,6-*O*-isopropylidene-D-*lyxo*-hexono-1,4-lactone (16).** The unsaturated mesylate **8** (13.91 g, 0.05 mol) was hydrogenated in the manner described earlier for compound **5a**. A solution of the crude product in DMF (50 mL) was treated with sodium azide (5.0 g, 0.077 mol) in the same way as described for **11a** to yield the pure azide **16**: 7.4 g (65%); mp 62.5–63.5 °C; $[\alpha]^{20}_D$ –197° (*c* 1.34, MeOH); $^1H$ NMR ($CDCl_3$) δ 1.36 (s, 6 H), 2.23 (dt, *J* = 13.5 and 9.5 Hz, 1 H), 2.56 (ddd, *J* = 3, 8.5, and 13.5 Hz, 1 H), 3.93 (dd, *J* = 8.5 and 7 Hz, 1 H), 4.07 (dd, *J* = 8.5 and 7 Hz, 1 H), 4.16 (td, *J* = 7 and 2 Hz, 1 H), 4.50 (dd, *J* = 9.5 and 8.5 Hz, 1 H), 4.54 (ddd, *J* = 9.5, 3, and 2 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 25.3 ($CH_3$), 25.5 ($CH_3$), 31.8 (C-3), 56.3 (C-2), 65.0 (C-6), 75.3 (C-4), 77.3 (C-5), 110.2 ($CMe_2$), 173.75 (C-1); IR (KBr) $\nu_{max}$ 2100 ($N_3$), 1790 $cm^{-1}$ (C=O). Anal. Calcd for $C_9H_{13}N_3O_4$: C, 47.57; H, 5.77; N, 18.49. Found: C, 47.6; H, 5.8; N, 19.0.

**2-Amino-2,3-dideoxy-5,6-*O*-isopropylidene-L-*lyxo*-hexonic Acid [5,6-*O*-Isopropylidene-4(*S*),5(*S*),6-trihydroxy-D-norleucine] (17a).** A suspension of azide **15a** (13.2 g, 0.058 mol) and

palladized charcoal (10%, 3.0 g) in ethanol–water (3:1, 240 mL) containing triethylamine (8.4 mL, 1 equiv) was hydrogenated overnight at 50 psi. The catalyst was removed by filtration and washed with ethanol–water (3:1) and water. The combined filtrate and washings were evaporated in vacuo, and ethanol was distilled in vacuo from the residue, which was then pulverized and triturated with ether to give the crude product **17a**, 10.66 g (84%). Recrystallization from 1,4-dioxane–$H_2O$ (19:1) gave pure **17a**: mp 190–192 °C; $[\alpha]^{20}_D$ −14.5° (*c* 1.85, $H_2O$); $^1H$ NMR ($D_2O$) δ 1.36 (s, 3 H), 1.43 (s, 3 H), 1.88 (dt, *J* = 15.5 and 9 Hz, 1 H), 2.10 (ddd, *J* = 3, 5.5, and 15.5 Hz, 1 H), 3.7–4.2 (m, 5 H), 4.7 (s, 4 H); IR (KBr) $\nu_{max}$ 3700–2500 (OH, $NH_3^+$), 1630–1595 $cm^{-1}$ ($CO_2^-$). Anal. Calcd for $C_9H_{17}NO_5$: C, 49.30, H, 7.82; N, 6.39. Found: C, 49.2; H, 7.8; N, 6.4.

**2-Amino-2,3-dideoxy-5,6-*O*-isopropylidene-D-*ribo*-hexonic Acid [5,6-*O*-Isopropylidene-4(*S*),5(*R*),6-trihydroxy-D-norleucine] (17b).** Azide **15b** (10.5 g, 0.046 mol) was reduced in the manner described for **15a**. The crude product [8.24 g (81%)] was recrystallized from 1,4-dioxane–water (19:1) to give **17b** as needles: mp 202.5–203.5 °C; $[\alpha]^{20}_D$ −12.5° (*c* 2.28, $H_2O$); $^1H$ NMR ($D_2O$) δ 1.36 (s, 3 H), 1.43 (s, 3 H), 1.92 (dt, *J* = 15.5 and 9 Hz, 1 H), 2.18 (ddd, *J* = 3, 5.5, and 15.5 Hz, 1 H), 3.6–4.15 (m, 5 H), 4.6 (s, 4 H); $^{13}C$ NMR ($D_2O$) δ 24.8 ($CH_3$), 26.15 ($CH_3$), 33.9 (C-3), 54.5 (C-2), 65.8 (C-6), 70.8 (C-4), 78.9 (C-5), 110.9 ($CMe_2$), 175.0 (C-1); IR (KBr) $\nu_{max}$ 3700–2500 (OH, $NH_3^+$), 1630–1595 $cm^{-1}$ ($CO_2^-$). Anal. Calcd for $C_9H_{17}NO_5$: C, 49.30; H, 7.82; N, 6.39. Found: 49.4; H, 7.8; N, 6.2.

**2-Amino-2,3-dideoxy-5,6-*O*-isopropylidene-D-*lyxo*-hexonic Acid [5,6-*O*-Isopropylidene-4(*R*),5(*R*),6-trihydroxy-L-norleucine] (20).** Similar reduction of azide **16** gave compound **20**: mp 191–193 °C; $[\alpha]^{20}_D$ +14° (*c* 1.12, $H_2O$); $^1H$ NMR ($D_2O$) δ 1.36 (s, 3 H), 1.43 (s, 3 H), 1.88 (dt, *J* = 15.5 and 9 Hz, 1 H), 2.10 (ddd, *J* = 15.5, 5.5, and 3 Hz, 1 H), 3.7–4.2 (m, 5 H), 4.7 (s, 2 H); $^{13}C$ NMR ($D_2O$) δ 24.9 ($CH_3$), 26.15 ($CH_3$), 34.45 (C-3), 54.6 (C-2), 66.0 (C-6), 70.8 (C-4), 79.1 (C-5), 110.9 ($CMe_2$), 175.2 (C-1); IR (KBr) $\nu_{max}$ 3700–2500 (OH, $NH_3^+$), 1630–1595 $cm^{-1}$ ($CO_2^-$). Anal. Calcd for $C_9H_{17}NO_5$; C, 49.30; H, 7.82; N, 6.39. Found: C, 49.5; H, 7.7, N, 6.4.

**2,3-Dideoxy-2-[(2,4-dinitrophenyl)amino]-5,6-*O*-isopropylidene-L-*lyxo*-hexono-1,4-lactone (18a).** A stirred, cooled (0 °C) solution of amino acid **17a** (1.095 g, 0.05 mol) in DMF (15 mL) was treated successively with potassium carbonate (0.77 g, 0.055 mol) and 2,4-dinitro-1-fluorobenzene (0.93 g, 0.05 mol). After 0.25 h, the cooling was removed and the mixture was allowed to stir at room temperature for a further 2.75 h, during which time its color changed from yellow to bright red. At the end of this time, oxalic acid dihydrate (760 mg, 0.06 mol) was added, followed by water (100 mL), and the resultant mixture extracted with ethyl acetate (2 × 100 mL). The combined, dried ($MgSO_4$) extracts were evaporated in vacuo to give a mixture (TLC) of mono- and disubstituted (1.99 g) derivatives. Column chromatography ($CHCl_3$–EtOAc, 6:1), followed by crystallization from methanol–water (3:1), gave the title product **18a**: 0.62 g (34%); mp 174.5–176 °C; $[\alpha]^{20}_D$ +153° (*c* 0.73, acetone); $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.36 (s, 6 H), 2.59 (dd, *J* = 6 and 9.5 Hz, 2 H), 3.7–4.5 (m, 4 H), 4.97 (td, *J* = 9.5 and 8 Hz, 1 H), 7.19 (d, *J* = 9 Hz, 1 H), 8.26 (dd, *J* = 3 and 9 Hz, 1 H), 8.78 (d, *J* = 8 Hz, 1 H), 8.80 (d, *J* = 3 Hz, 1 H). Anal. Calcd for $C_{15}H_{17}N_3O_8$: C, 49.05; H, 4.66; N, 11.44. Found: C, 49.0; H, 4.6; N, 10.9.

**2,3-Dideoxy-2-[(2,4-dinitrophenyl)amino]-5,6-*O*-isopropylidene-D-*ribo*-hexono-1,4-lactone (18b).** Analogous treatment of amino derivative **17b** gave title compound **18b**: mp 177–188 °C; $[\alpha]^{20}_D$ +110° (*c* 0.75, acetone); $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.35 (s, 3 H), 1.46 (s, 3 H), 2.59 (dd, *J* = 6 and 9.5 Hz, 2 H), 3.7–4.5 (m, 4 H), 5.04 (td, *J* = 9.5 and 8 Hz, 1 H), 7.23 (d, *J* = 9 Hz, 1 H), 8.28 (dd, *J* = 3 and 9 Hz, 1 H), 8.84 (d, *J* = 8 Hz, 1 H), 8.85 (d, *J* = 3 Hz, 1 H). Anal. Found: C, 49.5; H, 4.6; N, 11.3.

**2,3-Dideoxy-2-[(2,4-dinitrophenyl)amino]-5,6-*O*-isopropylidene-D-*lyxo*-hexono-1,4-lactone (21).** Treatment of compound **20** in the same way gave compound **21**: mp 175–177 °C; $[\alpha]^{20}_D$ −149° (*c* 0.75, acetone); $^1H$ NMR ($Me_2SO$-$d_6$) δ 1.34 (s, 6 H), 2.59 (dd, *J* = 6 and 9.5 Hz, 2 H), 3.7–4.5 (m, 4 H), 4.98 (td, *J* = 9.5 and 8 Hz, 1 H), 7.20 (d, *J* = 9 Hz, 1 H), 8.80 (d, *J* = 8 Hz, 1 H), 8.82 (d, *J* = 3 Hz, 1 H). Anal. Found: C, 49.1; H, 4.7; N, 11.3.

**2-Amino-2,3-dideoxy-L-*lyxo*-hexono-1,4-lactone Hydrochloride (19a).** A suspension of azide **15a** (1.136 g, 0.005 mol) in ethanol (18 mL) and 2 M HCl (6 mL) were hydrogenated overnight at 50 psi, in the presence of palladized charcoal (10%, 0.3 g). The catalyst was removed by filtration, and concentration of the filtrate in vacuo, followed by trituration of the residue with propan-2-ol (6 mL), afforded **19a** [0.867 g (88%)], recrystallization of which from methanol gave analytically pure material: mp 184–186 °C; $[\alpha]^{20}_D$ +65° (*c* 1.13, $H_2O$); $^1H$ NMR ($D_2O$) δ 2.75 (ddd, *J* = 8, 10.5, and 14 Hz, 1 H), 2.86 (ddd, *J* = 3.5, 9, and 14 Hz, 1 H), 3.7–4.1 (m, 3 H), 4.65 (dd, *J* = 9 and 10.5 Hz, 1 H), 4.8 (s, 5 H), 5.09 (ddd, *J* = 2, 3.5, and 8 Hz, 1 H); IR (KBr) $\nu_{max}$ 3700–2500 (OH, $NH_3^+$), 1795 $cm^{-1}$ (C=O). Anal. Calcd for $C_6H_{12}ClNO_4$: C, 36.47; H, 6.12; N, 7.09. Found: C, 36.8; H, 6.0; N, 6.9.

**2-Amino-2,3-dideoxy-D-*ribo*-hexono-1,4-lactone Hydrochloride (19b).** A solution of compound **17b** (0.552 g, 0.025 mol) in 1 M HCl (5 mL) was heated under reflux, with stirring, for 0.5 h. The mixture was evaporated to dryness in vacuo and the residue triturated with propan-2-ol (2 mL) to afford compound **19b** [0.402 g (81%)], recrystallization of which from ethanol–benzene gave material of analytical purity: mp 178–180 °C; $[\alpha]^{20}_D$ +26° (*c* 0.79, $H_2O$); $^1H$ NMR ($D_2O$) δ 2.62 (ddd, *J* = 8.5, 10.5, and 14 Hz, 1 H), 2.88 (ddd, *J* = 2.5, 9.5, and 14 Hz, 1 H), 3.79 (d, *J* = 5.5 Hz, 1 H), 3.80 (d, *J* = 6.5 Hz, 1 H), 3.9–4.3 (m, 1 H), 4.62 (dd, *J* = 9.5 and 10.5 Hz, 1 H), 4.7 (s, 5 H), 5.34 (ddd, *J* = 2.5, 3.5, and 8.5 Hz, 1 H). Anal. Found: C, 36.4; H, 6.0; N, 7.0.

**2-Amino-2,3-dideoxy-D-*lyxo*-hexono-1,4-lactone Hydrochloride (22).** Compound **22** was prepared in the manner described for compounds **19a** or **19b**, in comparable yield: mp 186–188 °C; $[\alpha]^{20}_D$ −66° (*c* 0.70, $H_2O$); $^1H$ NMR ($D_2O$) δ 2.76 (ddd, *J* = 14, 10.5, and 8 Hz, 1 H) 2.87 (ddd, *J* = 14, 9, and 3.5 Hz, 1 H), 3.7–4.1 (m, 3 H), 4.65 (dd, *J* = 10.5 and 9 Hz, 1 H), 4.8 (s, 5 H) 5.09 (ddd, *J* = 8, 3.5, and 2 Hz, 1 H). Anal. Found: C, 36.85; H, 6.1; N, 6.95.

**2-Amino-2,3-dideoxy-L-*lyxo*-hexonic Acid (23), Cu(II) Complex.** Protected amino acid **17a** (219 mg, 0.001 mol) in water (10 mL) was heated overnight under reflux. Concentration of the solution in vacuo yielded a glass, which could not be made anhydrous without considerable decomposition. The material was treated with a boiling solution of copper(II) acetate monohydrate (100 mg, 0.005 mol) in water (0.5 mL). The mixture was diluted with water (25 mL) and filtered and the filtrate evaporated partially in vacuo (~2 mL). The residual solution was brought to boiling, treated with absolute ethanol (2 mL), and then cooled. The resulting crude blue crystalline product (101 mg (48%)] was recrystallized from ethanol–water (1:1), affording the pure product: 86 mg (41%); mp 212–216 °C; $^1H$ NMR crude acid ($D_2O$) δ 1.95 (t, *J* = 4.5 Hz, 2 H), 3.4–3.9 (m, 5 H), 4.65 (s, 6 H). Anal. Calcd for $C_{12}H_{24}CuN_2O_{11}$: C, 34.33; H, 5.76; N, 6.67. Found: C, 34.0; H, 5.4; N, 6.6.

**2-Amino-2,3-dideoxy-D-*ribo*-hexonic Acid (24), Cu(II) Complex.** Treatment of compound **17b** in the above manner gave the product: 116 mg (55%); mp 210–214 °C; $^1H$ NMR crude acid ($D_2O$) δ 2.01 (t, *J* = 4.5 Hz, 2 H), 3.4–3.9 (m, 5 H), 4.65 (s, 6 H). Anal. Found: C, 34.8; H, 5.7; N, 6.8.

**2-Amino-2,3-dideoxy-D-*lyxo*-hexonic Acid (25), Cu(II) Complex.** Compound **20** in an analogous manner gave the product: 96 mg (46%); mp 212–216 °C; $^1H$ NMR crude acid ($D_2O$) δ 1.95 (dd, *J* = 9.5 Hz, 2 H), 3.5–4.0 (m, 5 H), 4.75 (s, 6 H). Anal. Found: C, 34.1; H, 5.0; N, 6.5.