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# VERSATILE SYNTHESIS OF DIHYDROXY γ AND δ AMINO ACIDS FROM CARBOHYDRATES

D. B. Tulshian*, A. F. Gundes and M. Czarniecki
Schering-Plough Research Institute
60 Orange St. Bloomfield, New Jersey, 07003, U.S.A.

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**Abstract:** The stereospecific syntheses of disubstituted derivatives of γ-aminobutanoic acid and δ-aminopentanoic acid are described starting from furanoses. The keys steps are the introduction of the amine in the form of an azide and the regiospecific ring opening with periodate. The methodology is readily applied to the synthesis of highly substituted analogs of homologated amino acids.

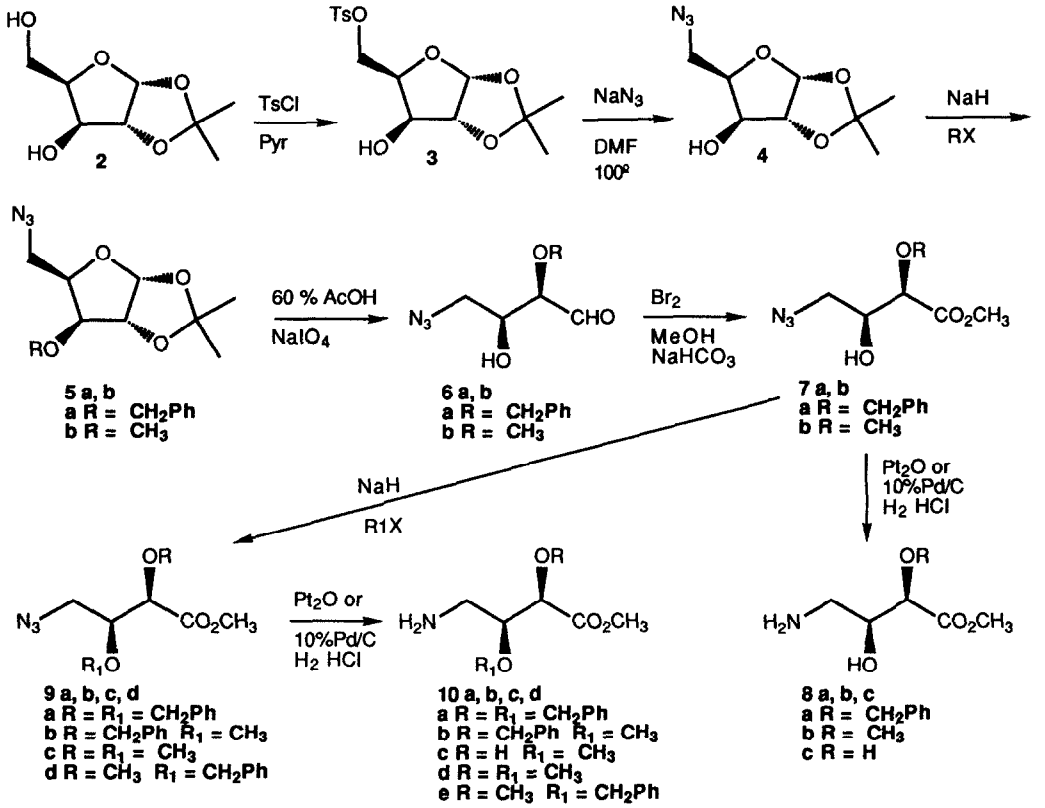
In the course of research towards therapeutically useful antihypertensive and antiasthmatic medicinal agents, the enantiospecific preparation of disubstituted butanoic and pentanoic amino acid analogs was undertaken.[1] The present study reports a versatile and general route to these compounds using readily available carbohydrates as convenient chiral starting materials.

As shown in **Scheme 1**, disubstituted amino acids with the 2*(S)*-3*(R)* configuration were prepared from the commercially available 1,2-*O*-isopropylidene-α-*D*-xylofuranoside, **2**. Treatment of **2** with *p*-toluenesulphonyl chloride produced **3**[2] almost exclusively. Less than 10% of ditosyl derivative was also isolated from this reaction. Displacement[3] of the tosyl group of **3** with sodium azide occurred at 100° C in dimethylformamide in better then 90% yield. The hydroxyl at C-3 was then functionalized as either a benzyl or methyl ether using benzyl bromide or methyl iodide and sodium hydride in tetrahydrofuran. Hydrolysis of the 1,2-*O*-isopropylidene group of **5** with 60% aqueous acetic acid, and sodium-metaperiodate cleavage of this crude product gave the aldehyde **6**. The careful oxidation of **6** with bromine/sodium bicarbonate[4] produced desired ester **7** in 85% yield. The use of excess sodium bicarbonate or a prolonged reaction time during the oxidation led to racemization of the aldehyde.

Ester **7** was the most versatile intermediate for conversion to various 2*(S)*-3*(R)* disubstituted aminobutyric esters. The free hydroxyl group of **7** can be functionalized to desired substituents, the benzyl group can be removed, and the resulting hydroxyl group can be derivatized. Reduction of azidoester **7** was carried out either with platinum oxide or 10% palladium on charcoal in the presence of hydrochloric acid to produce the corresponding amino esters as their salts. Reduction of benzyloxy substituted ester **7a** with platinum oxide gave **8a**, whereas reduction with 10% palladium on charcoal produced 2*(S)*-3*(R)*-dihydroxy aminobutyric ester **8c**. The 3*(R)* methoxy aminobutyric ester **8b** was obtained under either of these reduction conditions from **7b**. Treatment of both **7a** and **7b** with benzyl bromide or methyl iodide produced the corresponding bis protected compound **9** which was reduced as described to produce various amino esters, represented by structure **10.**

Synthesis of 2*(R)*-3*(R)* disubstituted aminobutyric acid began with 1,2,4,5-di-*O*-isopropylidene-α-*D*-allofuranoside **11** (**Scheme 2**). Protection of the hydroxyl group at C-3 as a benzyl or methyl ether was performed as described for **4.** Selective deprotection of the 5,6-*O*-isopropylidene of **12** with dilute sulfuric acid in methanol gave the diol which was then cleaved with sodium metaperiodate.[5] The combined yield of this two step/one pot reaction was about 80%. Aldehyde **13** was reduced with sodium borohydride to **14,** which on reaction with *p*-toluenesulphonyl chloride produced **15** in better then 85% yield. The tosyl group was then

**Scheme 1**

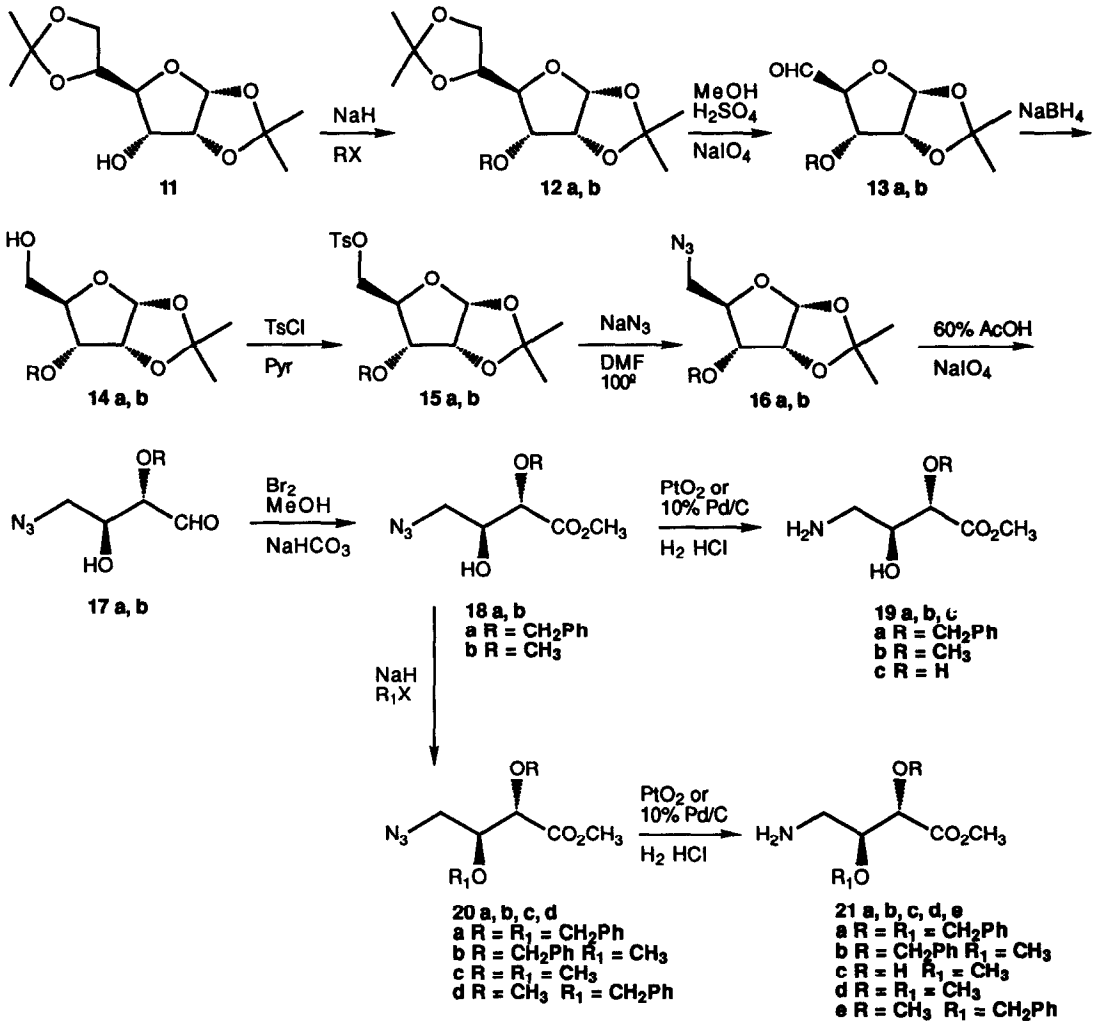



displaced with sodium azide. The azide **16** was then converted to the corresponding amino esters using the reaction sequence described for compound **5**.

The 3(*R*)-4(*R*) disubstituted aminopentanoic acids were prepared from methyl-2-deoxy-*D*-ribofuranoside **22**[6] (see **Scheme 3**). The primary hydroxyl group was selectively converted to a tosyl group as described for xylose derivative **2**. Conversion of this tosyl derivative to azide **24** was achieved as described above in 70% yield. The anomeric mixture of **24** can be separated easily by flash column chromatography. For the present work, however, this separation is not generally required, except as an aid to spectral analysis. Sequential alkylation of the hydroxyl group yields **25**, hydrolysis to aldehyde **26** and oxidation with bromine/sodium bicarbonate gave ester **27**. These azidoesters were then converted to various substituted amino esters, **28** and **30**.

In summary a versatile method for the preparation of chiral 2,3 disubstituted γ and δ amino acids from carbohydrates has been presented.[7] These amino acid homologs can be broadly utilized in the synthesis of biologically active molecules. The highly selective functionalization of specific hydroxyls suggests the feasibility of further stereospecific functional group manipulation. Finally, the generality of the methods cited in the three examples indicates that extension of these techniques to other problems involving chiral substituted ω-aminoacid derivatives should be possible.

**Scheme 2**




## References and Notes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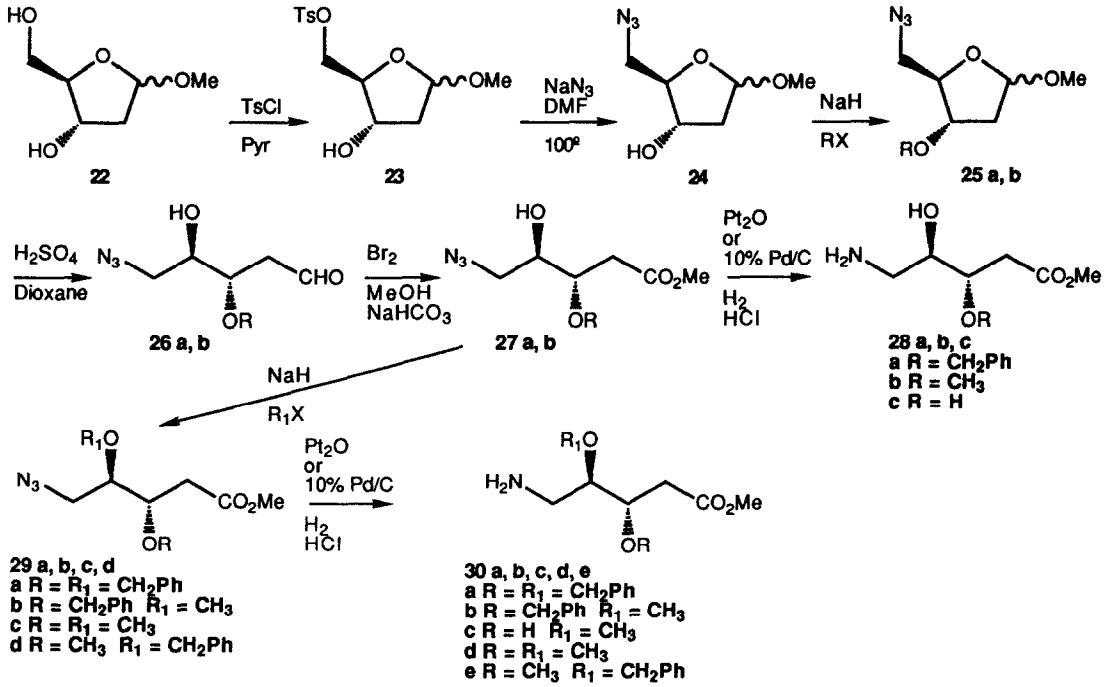
**Scheme 3**




**References and Notes (cont.)**

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6. Deriaz, R. E.; Overend, W. G.; Stacey, M.; Wiggins, L. F. *J. Chem. Soc.* **1949**, 2836.
7. All new compounds were characterized by $^1$H NMR and high resolution MS. Data of selected key intermediates are reported below: **5a** $^1$H NMR ($CDCl_3$, 200 MHz) δ 1.32 and 1.48 (6 H, 2s, $C(CH_3)_2$), 3.55 (2 H, ABX, $J_{A,B}$= 12.5 Hz, $J_{A,X}$=$J_{B,X}$=6.0 Hz, $CH_2N_3$), 3.65 (1 H, d, $J_{1,2}$=3.5 Hz, H-2), 3.92 (1 H, d, $J_{3,4}$=3.9 Hz, H-3), 4.30 (1 H, m, H-4), 4.52 and 4.68 (2 H, AB, $J_{A,B}$=12.0 Hz, $OCH_2Ph$), 5.92 (1 H, $J_{1,2}$=3.5 Hz, H-1), 7.35 (5H, m, $C_6H_5$); **7a** $^1$H NMR ($CDCl_3$, 200 MHz), d 3.50 (2 H, ABX, $J_{A,B}$=12.70, $J_{A,X}$=$J_{B,X}$=6.6 Hz, $CH_2N_3$), 3.80 (3 H, s, $CO_2CH_3$), 4.05 (2 H, m), 4.45 and 4.85 (2 H, AB, $J_{A,B}$=12.5 Hz, $OCH_2Ph$). 7.32 (5H, m, $C_6H_5$); **16a** $^1$H NMR ($CDCl_3$, 200 MHz), δ 1.35 and 1.42 (6 H, 2s, $OC(CH_3)_2$), 3.25 (1 H, dd, $J_{5,5}$=13.2, $J_{4,5}$= 4.8 Hz, H-5), 3.65 (1 H, dd, $J_{4,5'}$=4.0 Hz, H-5'), 4.2 (1 H, m, H-4), 4.60 (1 H, t, $J_{1,2}$=$J_{2,3}$=5.0 Hz, H-2), 4.55 and 4.80 (2 H, AB, $J_{A,B}$=12.5 Hz, $OCH_2Ph$), 4.78 (1 H, dd, $J_{3,4}$=10 Hz, $J_{2,3}$=5.0 Hz, H-3), 5.75 (1 H, d, $J_{1,2}$=5.0 Hz, H-1), 7.4 (5 H, m, $C_6H_5$); **16b** $^1$H NMR ($CDCl_3$, 200 MHz) δ 1.40 and 1.60 (6 H, 2s, $C(CH_3)_2$), 3.32 (1 H, dd, $J_{5,5'}$=12.7 Hz, $J_{4,5}$=5.0 Hz, H-5), 3.50 (3 H, s, $OCH_3$), 3.75 (1 H, dd, $J_{4,5'}$=4.5 Hz, H-5'), 3.60 (1 H, dd, $J_{3,4}$=10 Hz, $J_{2,3}$=4.5 Hz, H-3) 4.15 (1 H, m, H-4), 4.70 (1 H, t, $J_{1,2}$=$J_{2,3}$=4.5 Hz, H-2), 5.80 (1 H, d, $J_{1,2}$=4.5 Hz, H-1); **18a** $^1$H NMR ($CDCl_3$, 200 Hz) δ 3.45 (2 H, m, $CH_2N_3$), 3.70 (3 H, s, $COOCH_3$), 4.10 (2H, m ), 4.48 and 4.78 (2 H, AB, $J_{A,B}$=12.70 Hz, $OCH_2Ph$), 7.35 (5 H, m, $C_6H_5$); **29c** $^1$H NMR ($CDCl_3$ 200 MHz) δ 2.35 (2H, m, $CH_2CO_2CH_3$), 3.45 (2H, ABX, $J_{A,B}$ = 12.5 Hz, $J_{AX}$ = $J_{BX}$ = 6.20 Hz, $CH_2N_3$), 3.52, 3.56 (6H, 2s, 2 $OCH_3$), 3.82 (3H, s, $CO_2CH_3$), 4.15-4.25 (2H, m).