to afford a quantitative conversion to (±)-α- and (±)-β-cedrene (80:20). They could be separated by GLC (column B, 146 °C): ^{1}H NMR δ 0.82 (3 H, d, J = 6.5 Hz, CH_3CH), 0.92 (3 H, s, *endo*-CH_3), 0.98 (3 H, s, *exo*-CH_3), 5.15 (0.8 H, br s, HC=C, α), 4.49 (0.2 H, br s, CH_2=C, β) ppm; mass spectrum M* 204.

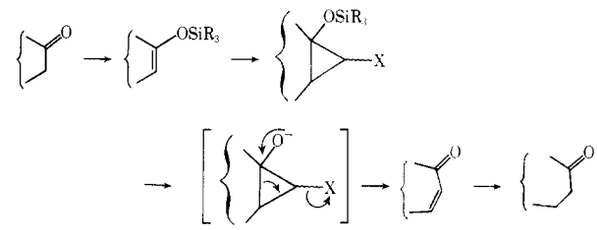
These results compared favorably with an authentic sample of cedrol, which under the conditions described above afforded the α- and β-cedrenes in an 83:17 ratio. The spectral features of the synthetic cedrene were in excellent agreement with an authentic sample of α-cedrene (Aldrich) shown by GLC and NMR analysis to contain 14% of the β isomer

Acknowledgment. We are grateful to Memorial University of Newfoundland for financial support of this research.

Registry No.—**1**, 22567-43-7; **2**, 22567-44-8; **4** epimer 1, 65391-62-0; **4** epimer 2, 65391-63-1; **5** epimer 1, 65391-64-2; **5** epimer 2, 65391-65-3; 5-DNP, 65442-01-5; **6** epimer 1, 50896-63-4; **6** epimer 2, 50896-62-3; **7**, 4582-61-0; **8b**, 65378-59-8; **9**, 65378-60-1; **10**, 65378-61-2; **10** HCl, 65378-62-3; **11**, 65378-63-4; 6-methyl-5-hepten-2-one, 110-93-0; 6-methyl-5-hepten-2-ol, 1569-60-4; *p*-toluenesulfonyl chloride, 98-59-9; 2-bromo-6-methyl-5-heptene, 4434-77-9; cyclopentadiene, 542-92-7; sodium cyclopentadiene, 4984-82-1; cyclopentadienyl bromide, 41851-49-4; lithium cyclopentadiene, 16733-97-4; trimethylsilylcyanide, 7677-24-9; (±)-*epi*-cedrol, 65391-66-4; (±)-β-cedrene, 65450-98-8.

References and Notes

(1) G. Stork and R. Breslow, *J. Am. Chem. Soc.*, **75**, 3291, 3292 (1953); Pl. A. Plattner, A. Fürst, A. Eschenmoser, W. Keller, H. Klau, St. Meyer, and M. Rosner, *Helv. Chim. Acta*, **36**, 1845 (1953); Pl. A. Plattner, A. Fürst, St. Meyer, and W. Keller, *ibid.*, **37**, 266 (1954).
(2) P. Yates and G. F. Field, *J. Am. Chem. Soc.*, **82**, 5764 (1960).
(3) R. Kaiser and P. Naegeli, *Tetrahedron Lett.*, 2009 (1972); A. N. Singh, A. D. Upadhye, V. V. Mhasker, S. Dev, A. V. Pol, and V. G. Naik, *Tetrahedron*, **30**, 3689 (1974).
(4) G. Stork and F. H. Clarke, Jr., *J. Am. Chem. Soc.*, **77**, 1073 (1955); **83**, 3114 (1961).
(5) E. J. Corey, N. N. Girotra, and C. T. Mathew, *J. Am. Chem. Soc.*, **91**, 1557 (1969); T. G. Crandall and R. G. Lawton, *ibid.*, **91**, 2127 (1969); E. Demole, P. Enggist, and C. Borer, *Helv. Chim. Acta*, **54**, 1845 (1971); N. H. Anderson and D. D. Syrdal, *Tetrahedron Lett.*, 2455 (1972); E. J. Corey and R. D. Balanson, *Tetrahedron Lett.*, 3153 (1973); P. T. Lansbury, V. R. Haddon, and R. C. Stewart, *J. Am. Chem. Soc.*, **96**, 896 (1974).
(6) A portion of our work has appeared in preliminary form: E. G. Breitholle and A. G. Fallis, *Can. J. Chem.*, **54**, 1991 (1976); presented in part at the International Symposium on Stereochemistry, Abstract M1, Kingston, Ontario, Canada, June 27–July 2, 1976. At the outset it appeared that α-pompene was also a member of this tricyclic family; however, its structure has been revised; A. Matsuo, T. Maeda, M. Nakayama, and S. Hayashi, *Tetrahedron Lett.*, 4131 (1973); A. Matsuo, H. Nozak, M. Nakayame, Y. Kushi, S. Hayashi, and N. Kaminjo, *Tetrahedron Lett.*, 241 (1975).
(7) R. G. Carlson, *Annu. Rep. Med. Chem.*, **9**, 270 (1974); W. Oppolzer, *Angew. Chem., Int. Ed. Engl.*, **16**, 10 (1977).
(8) H. O. House and T. H. Cronin, *J. Org. Chem.*, **30**, 1061 (1965).
(9) S. McLean and P. Haynes, *Tetrahedron*, **21**, 2329 (1965); see also J. Backes, R. W. Hofmann, and F. W. Steuber, *Angew. Chem., Int. Ed. Engl.*, **14**, 553 (1975).
(10) Cf. E. J. Corey and R. S. Glass, *J. Am. Chem. Soc.*, **89**, 2600 (1967); A. Krantz and C. Y. Lin, *ibid.*, **95**, 5662 (1973).
(11) O. Wallach, *Justus Liebigs Ann. Chem.*, **275**, 171 (1893); J. Mori, *Tetrahedron*, **31**, 3011 (1975).
(12) R. B. King and F. G. A. Stone, *Inorg. Synth.*, **7**, 99 (1963).
(13) Attempted use of thallium cyclopentadiene was unsuccessful.
(14) We are grateful to A. W. McCulloch and J. A. Walter, National Research Council of Canada, Halifax, Nova Scotia, for obtaining this spectrum.
(15) G. Fachinett, F. Pictra, and A. Marsili, *Tetrahedron Lett.*, 393 (1971); M. A. McKinney and P. P. Patel, *J. Org. Chem.*, **38**, 4059 (1973).
(16) D. A. Evans, G. L. Carroll, and L. K. Truesdale, *J. Org. Chem.*, **39**, 914 (1974).
(17) This sequence would be improved if formation of the unwanted ketone could be suppressed. This should be feasible as outlined, since the carbon bearing oxygen is locked in position in the starting ketone and final product. After completion of the synthesis but before this was a workable alternative, others reported a closely related ring expansion for the system X = H using ferric chloride which should be applicable to the present case.[18]



(18) Y. Ito, S. Fujii, and T. Saegusa, *J. Org. Chem.*, **41**, 2073 (1976); cf. G. Stork and T. L. MacDonald, *J. Am. Chem. Soc.*, **97**, 1264 (1975).
(19) E. V. Rudloff, *Can. J. Chem.*, **39**, 1860 (1961).
(20) G. Brieger, *J. Am. Chem. Soc.*, **85**, 3783 (1963).

Synthesis of Garosamine and of Related Amino Sugars. An Efficient Tetrahydrooxazine Ring Opening

John J. Wright* and Charles L. Luce

Chemical Research Schering Corporation, Bloomfield, New Jersey 07003

Received October 27, 1977

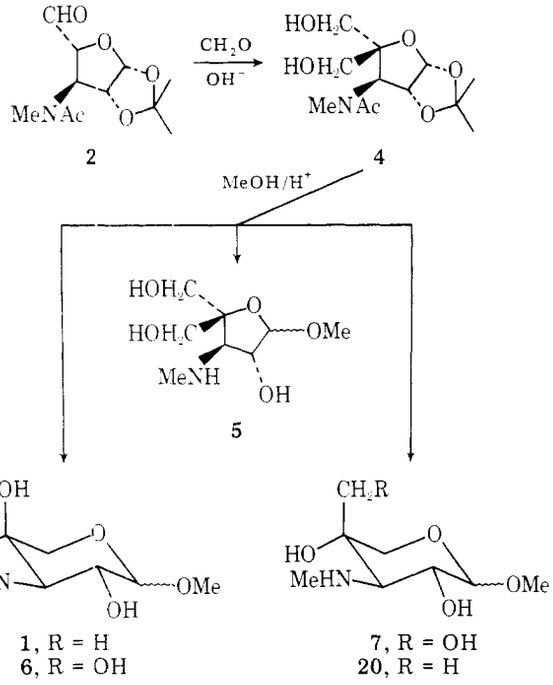
Garosamine, a component of the antibiotic gentamicin, and a series of related amino sugars have been synthesized from glucose by a stereospecific route involving a versatile tricyclic intermediate. A new oxidative tetrahydrooxazine ring-opening reaction is also reported.

The synthesis of branched chain amino sugars has been the focus of attention of a number of research groups in recent years because of the common occurrence of these compounds in nature in association with antibiotics. Synthetic approaches to these compounds have usually employed the addition of organometallic reagents, diazoalkanes, and enolate salts to cyclic ketones with varying degrees of stereochemical control. Such an approach was used in a previous synthesis of the methyl glycoside of garosamine (**1**),[1] a component monosaccharide of the gentamicin antibiotics.[2] Because of our interest in synthetic approaches to aminoglycoside antibiotics,[3] we required an efficient and stereospecific synthesis of garosamine and of structurally related amino sugars. We wish to report such a synthesis and also the development in the course of this work of a novel tetrahydrooxazine ring-opening reaction.

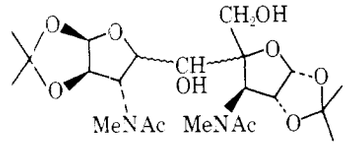
We had observed in a related study that the aldehyde **2** is prone to undergo aldol condensations leading, for example, after borohydride reduction of the initially formed aldol condensation product, to the dimeric compound **3**, of undetermined stereochemistry at position 4 of both furanosyl rings. Exploitation of the reactivity of a related aldehyde in the synthesis of apiose has been reported.[4] Our planned synthesis is outlined in Scheme I.

0022-3263/78/1943-1968$01.00/0

Scheme I



In view of the above observation, the aldehyde **2** was expected to undergo aldol condensation with formaldehyde under mildly alkaline conditions to give, after reduction of the intermediate β-hydroxy aldehyde, the diol **4**. Methanolysis (6 N HCl) of **4** was expected to give an equilibrium mixture of the furanosyl and pyranosyl glycosides **5**, **6**, and **7** in which

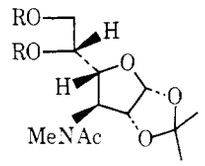


3

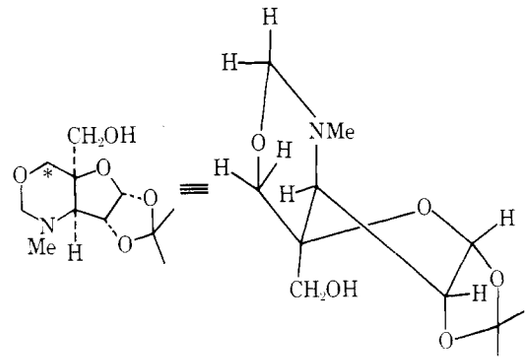
6, the pyranosyl anomeric mixture with the hydroxymethyl group in an equatorial position, was expected to predominate. It should be noted that the starting aldehyde epimeric at C-4 would serve equally well for the purpose as the same enolate ion would be involved in the aldol condensation step.

The unknown amino sugar **6** formally corresponds to methyl garosaminide in which the C-methyl group is functionalized with a hydroxyl group and constituted in itself a desired target compound.

1,2:5,6-Diisopropylidene-3-methylamino-3-*N*-acetyl-α-D-galactofuranoside (**8**) was prepared in high overall yield from diisopropylidene glucose by modification of existing routes.[5,6] Selective hydrolysis in aqueous acetic acid of the 5,6-isopropylidene group gave the crystalline diol **9**, mp 114–118 °C, in 82% yield. Periodate oxidation of the diol gave aldehyde **2** which was not isolated but which was treated with excess aqueous formaldehyde under alkaline conditions (pH 10.5). Over several hours at 40 °C a clean conversion into a single product (mp 79–80 °C) was observed in 90% yield after crystallization. Examination of the mass and ^{1}H NMR spectra allowed the assignment of structure **10** to this material. The expected aldol reaction clearly took place and was followed by cross-Cannizzaro reduction with excess formaldehyde to generate diol **4**. Under the mildly basic conditions of this reaction, neighboring group-assisted hydrolysis of the acetamide group occurred to give the methylamino compound **12** which condensed rapidly with excess formaldehyde to give **10**. In accordance with this mechanism, the diol intermediate **4** could be obtained in high yield by keeping the pH near 8. When sodium borohydride was added to the reaction mixture some

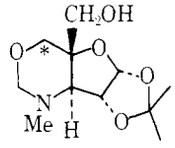


8, R = R = isopropylidene
9, R = R = H

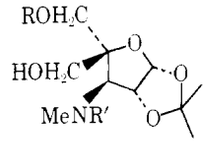


10

of the dimethylamino analogue **13** was obtained, mp 64–66 °C.



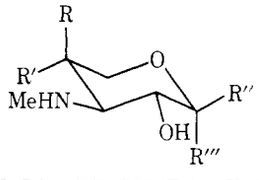
11



12, R = R′ = H
13, R = H; R′ = Me
23, R = tetrahydropyranyl; R′ = H

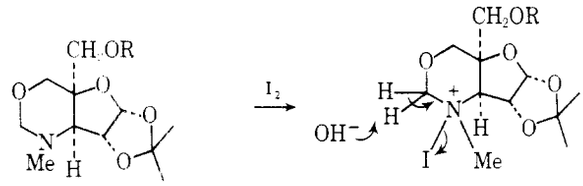
Although two isomeric forms of the tricyclic alcohol **10** having either a cis or a trans ring junction are possible in principle, examination of models and of the ^{1}H NMR spectrum strongly suggested that only the cis ring junction would be formed, as drawn, because of constraints imposed by the 1,2-isopropylidene group. The small coupling constant (~0.5 Hz) between H-2 and H-3 in **10** and in all the 1,2-isopropylidene derivatives in this series is characteristic of a T_2[3] twist conformation of the furanose ring[7] in which the torsional angle between H-2 and H-3 is close to 90°. Only the hydroxymethyl group cis to the amine group can be involved in the tetrahydrooxazine ring when the furanose has this conformation. Proof of this assignment was obtained by chemical correlation vide infra. The remarkable ease of hydrolysis of the amide **4** presumably arises from catalytic participation by the neighboring *cis*-hydroxymethyl group.

Methanolysis (6 N HCl in methanol) of **4** gave an anomeric mixture of the desired pyranosides (**14** and **15**) which were separable by partition chromatography on silica gel in a combined yield of 70%. Proof of the stereochemistry at position 4 of both anomers was obtained from circular dichroism measurements of the cuproammonium complexes (TaCu) in solution. Only vicinal amino alcohols can form strong complexes with tetramine copper[8] and the sign of the Cotton effect

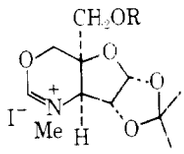


14, R = OH; R′ = CH_2OH; R″ = H; R‴ = OMe
15, R = OH; R′ = CH_2OH; R″ = OMe; R‴ = H
16, R = CH_2OH; R′ = OH; R″ = H; R‴ = OMe
17, R = CH_2OH; R′ = OH; R″ = OMe; R‴ = H
18, R = OH; R′ = Me; R″ = H; R‴ = OMe

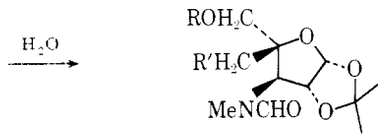
Scheme II



10, R = H
21, R = tetrahydropyranyl
24, R = CONHPh



29, R = H
30, R = tetrahydropyranyl
31, R = CONHPh



19, R = H; R′ = OH
22, R = tetrahydropyranyl; R′ = OH
25, R = CONHPh; R′ = OH
26, R = CONHPh; R′ = I
27, R = CONHPh; R′ = H

at 280 nm is diagnostic for the chirality of the complex.[9] The value for $[\theta]_{280}$ of −7100 obtained for **14** and of −5350 for **15** corresponds in each case to a δ chelate in which the vicinal amino and alcohol groups form a positive torsional angle. Whereas in **14** and **15** both possible sites of complexation would lead to such a chelate, both components of the alternative anomeric mixture **16** and **17** have the alternative stereochemistry at C-4 and formation of both λ and δ chelates would be possible for each anomer making approximately equal and opposite contributions to the magnitude of the Cotton effect. This would lead in each case to a value for $[\theta]_{280}$ near zero. In agreement with the assignment of structures **14** and **15** to the products, a value for $[\theta]_{280}$ of −7960 was obtained for β-methyl garosaminide (**18**) obtained from natural sources.

The ready formation of the tricyclic alcohol **10** offered the opportunity to modify selectively the groups corresponding to the geminal hydroxymethyl groups of the intermediate **4**, thereby providing a stereospecific route to a number of branched chain amino sugars. For this purpose procedures were required to open the tetrahydrooxazine ring in the presence of the isopropylidene group. Attempts to hydrolyze this ring selectively under mildly acidic conditions were not successful. In addition, methanolysis of **10** in 6 N methanolic hydrochloric acid did not provide the expected methyl glycosides **14** and **15** but gave products which incorporated the *O,N*-methylene group originally derived from formaldehyde either through retention of the tetrahydrooxazine ring or from initial cleavage to formaldehyde followed by recondensation.

It was necessary, therefore, to devise a method to open the tetrahydrooxazine ring under neutral or mildly basic conditions. This was achieved by the action of iodine and sodium acetate in aqueous methanol. The oxidative cleavage of **10** by this method proceeded smoothly under mildly basic conditions to give the ring-opened *N*-formyl compound **19** in 91% yield in 30 min at room temperature. Prolonged treatment led to the formation of traces of the product of formamide hydrolysis. This reaction appears to be general for related systems, proceeding efficiently also in the five-membered oxazolidine ring system.[10] The postulated mechanism is outlined in Scheme II.

Methanolysis of the *N*-formyl derivative **19** under conditions identical to that of **4** gave rise to the same anomeric mixture of methyl glycosides **14** and **15**.

The stereochemistry of the ring junction in the tricyclic alcohol **10** was determined by conversion of **10** into methyl garosaminide. Formal transformation of the methylene group marked with an asterisk in **10** into a methyl group would lead, after methanolysis, to methyl garosaminide (**1**) if the ring junction were cis as shown. If the junction were trans, the unknown isomer **20** would result. To this end, the hydroxymethyl group in **10** was first blocked as its tetrahydropyranyl ether to give **21** as an inseparable diastereomeric mixture. Oxidative ring cleavage provided the *N*-formyl analogue **22** in 91% yield after chromatography. Attempts to convert the hydroxymethyl group generated in this reaction into a methyl group proved difficult because of steric hindrance to displacement reaction at that neopentyl-like site. Thus, lithium triethylborohydride reduction of the mesylate derivative proved unsuccessful. Similarly attempted displacement of the mesylate group with iodide ion led to recovered starting material and treatment with hydrazine gave only the product of sulfur–oxygen cleavage of the sulfonate group and de-*N*-formylation (**23**).

A successful displacement was, however, achieved in moderate yield with triphenylphosphite methiodide, although acidic conditions generated by this reagent led to hydrolysis of the tetrahydropyranyl ether blocking group. In an alternate procedure, the alcohol group in **10** was blocked as the phenylcarbamate by reaction with phenyl isocyanate in pyridine and oxidative ring cleavage then proceeded smoothly as before to give the required *N*-formyl derivative **25**. In this compound, as in all the *N*-formyl derivatives, the ^{1}H NMR spectrum reflected the presence in solution of nearly equal proportions of the two amide rotamers. Treatment of **25** with triphenylphosphite methiodide in dry dimethylformamide at 80 °C gave the iodide **26** in 44% yield and reduction of this material with tri-*n*-butylstannane proceeded smoothly in benzene at reflux to provide the desired methyl analogue **27**.

Attempts to generate the iodo derivative **26** directly from **24** by oxidation with iodine in aprotic solvents via displacement on carbon of a postulated intermediate imminium salt (**31**) were unsuccessful. This was presumably due in part to the considerable steric hindrance at the site of displacement.

As the phenylcarbamate group proved resistant to hydrolysis by methanolic hydrochloric acid, compound **27** was deblocked in two successive stages; treatment with ethanolic hydrazine hydrate was followed by methanolysis. The product obtained in 80% yield was an anomeric mixture of α- and β-methyl garosaminides (**1**) identical with authentic material in all chromatographic and analytical aspects.

This transformation constitutes a stereospecific synthesis of garosamine and also confirms the initial assignment of cis stereochemistry to the ring junction in **10**. Clearly chemical manipulation of this tricyclic intermediate will lead therefore to a variety of branched chain amino sugars of known relative (and absolute) stereochemistry of utility in the synthesis of new aminoglycoside antibiotics.

Experimental Section

^{1}H-NMR spectra were obtained at 60 or 100 MHz using either a Varian A60A or a XL 100-15 spectrometer. Chemical shifts in $CDCl_3$ are reported in ppm downfield from internal Me_4Si. IR spectra were recorded with either a Perkin-Elmer 221 or an Infracord 137 spectrometer. Mass spectra were recorded with a Varian CH5 spectrometer. CD spectra were recorded on a Cary 61 spectrometer.

Preparation of *N*-Methyl-*N*-acetyl-3-amino-3-deoxy-1,2:5,6-diisopropylidene-α-D-galactofuranose (8). *N*-Acetyl-3-

amino-3-deoxy-1,2:5,6-diisopropylidene-α-D-galactofuranose (5 g) was dissolved in dry DMF (20 mL). Sodium hydride (750 mg) and methyl iodide (3.5 g) were added and the whole solution was stirred for 5 h. Ethanol was added until effervescence ceased, the solution was filtered, and the filtrate was reduced to dryness under reduced pressure. The residue was taken up in chloroform and filtered and ether was added to induce crystallization of the title compound (4.5 g, 85%): mp 140–141 °C; $[\alpha]^{26}_D$ +8.5° (0.4, methanol); NMR ($CDCl_3$) δ 1.32, 1.38, 1.45, 1.58 (4 s, 12 H, isopropylidene CH_3,s), 2.09 (s, 3 H, $COCH_3$), 3.08 (s, 3 H, NCH_3), 4.84 (dd, 1 H, J = 4, 1 Hz, H-2), 6.08 (d, 1 H, J = 4 Hz, H-1); mass spectrum m/e 315 (M^+), 300 ($M - 15$)$^+$. Anal. Calcd for $C_{15}H_{25}NO_6$: C, 57.2; H, 7.9; N, 4.5. Found: C, 56.9; H, 7.8; N, 4.62.

Preparation of *N*-Methyl-*N*-acetyl-3-amino-3-deoxy-1,2-iospropylidene-α-D-galactofuranose (9). *N*-Methyl-*N*-acetyl-3-amino-3-deoxy-1,2:5,6-di-isopropylidene-α-D-galactofuranose (10.0 g) was dissolved in 50% aqueous acetic acid and left at room temperature for 18 h. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel in 7.5% methanol in chloroform to give the title compound (7.6 g, 87%): mp 114–118 °C; $[\alpha]^{26}_D$ +23.4° (0.3, $CHCl_3$); NMR ($CDCl_3$) δ 1.33 (s, 3 H, C-CH_3), 1.58 (s, 3 H, $COCH_3$), 4.9 (d, 1 H, J = 4 Hz, H-2), 6.08 (d, 1 H, J = 4 Hz, H=1); mass spectrum m/e 275 (M^+). Anal. Calcd for $C_{12}H_{21}NO_6$: C, 52.4; H, 7.6; N, 5.1. Found: C, 52.3; H, 7.9; N, 5.0.

Starting material (1.1 g) was also recovered.

4-Hydroxymethyl-3,5-*O*,*N*-methylene-1,2-isopropylidene-3-methylamino-3-deoxy-α-D-xylofuranoside (10). *N*-Acetyl-*N*-methyl-1,2-isopropylidene-3-amino-3-deoxy-α-D-galafuranoside (9) (7.6 g) was dissolved in water (70 mL) and sodium metaperiodate (6.23 g) was added. After 20 min, ethylene glycol (0.5 mL) was added followed after 10 min by an 37% aqueous solution of formaldehyde (40 mL). Sodium bicarbonate (2.5 g) was added and the pH of the resulting solution was adjusted to 10.5 with 1 N sodium hydroxide solution. After 4 h at 40 °C, a further 20 mL of formaldehyde solution was added and the reaction mixture was left at 40 °C for a further 30 min. The solution was extracted with chloroform to give the title compound essentially pure (6.7 g). Chromatography on silica gel gave analytical grade material (6.1 g, 90%): mp 79–80 °C (from diethyl ether–hexane); $[\alpha]^{26}_D$ −52.9°; NMR ($CDCl_3$) δ 1.33 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 2.34 (s, 3 H, N-CH_3), 2.48 (s, 1 H, OH), 2.81 (broad s, 1 H, H-3), 4.68 (broad d, 1 H, J = 5 Hz, H-2), 6.07 (d, 1 H, J = 5 Hz, H-1); mass spectrum m/e 245 (M^+), 230 ($M - 15$)$^+$. Anal. Calcd for $C_{11}H_{19}NO_5$: C, 53.9; H, 7.8; N, 5.7. Found: C, 53.6; H, 8.0; N, 5.5.

4-Hydroxymethyl-1,2-isopropylidene-3-*N*-formyl-3-*N*-methyl-3-amino-3-deoxy-α-D-arabinofuranoside (19). The tricyclic alcohol (10) (2.9 g) was dissolved in 25% aqueous methanol and treated with sodium acetate (15 g) and iodine (15 g). After 30 min, the reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with an aqueous solution of sodium thiosulfate and water and dried. The whole was concentrated to dryness to give the title compound (2.3 g, 91%) as a gum: $[\alpha]^{26}_D$ +30.6° (0.3, ethanol); NMR ($CDCl_3$) 1.33 (s, 3 H, C-CH_3), 1.58 (s, 3 H, c-CH_3), 2.92, 3.12 (2 s, 3 H, N-CH_3, rotamers); 4.2 (m, 1 H, H-3), 4.9, 5.14 (2 dd, 1 H, J = 1.5, 4 Hz, H-2, rotamers), 5.99, 6.08 (2 d, 1 H, H-1, rotamers), 8.1 (s, 1 H, CHO); mass spectrum m/e 261 (M^+). Anal. Calcd for $C_{11}H_{19}NO_6$: C, 50.6; H, 7.3; N, 5.4. Found: C, 50.4; H, 7.4; N, 5.1.

Methyl 3-Methylamino-3-deoxy-4-hydroxymethyl-2- and β-L-arabinopyranoside. The *N*-formyl derivative (19) (2.1 g) was heated at reflux in 6 N methanolic hydrochloric acid for 3 h. The solvent was removed under vacuum and the residue was chromatographed on silica gel in the lower phase of a chloroform–methanol–10% ammonium hydroxide (2:1:1) solvent mixture to give first the α glycoside as a gum (0.54 g) (15): $[\theta]_{280}$ (TaCu) −5350; 100 MHz NMR (D_2O) δ 2.45 (s, 3 H, NCH_3), 4.52 (s, 3 H, OCH_3), 4.25 (d, 1 H, J = 8 Hz, H-1); mass spectrum m/e 207 (M^+), 208 ($M + 1$)$^+$.

Subsequently isolated also as a gum was the β glycoside (14) (0.69 g): $[\theta]_{280}$ (TaCu) −7100; 100 MHz NMR (D_2O) δ 2.45 (s, 3 H, NCH_3), 2.72 (d, 1 H, J = 10.5 Hz, H-3), 3.41 (s, 3 H, OCH_3), 3.77 (dd, 1 H, J = 4, 10.5 Hz, H-2), 3.8 (d, 1 H, J = 12.5 Hz, H-5 eq), 4.75 (d, 1 H, J = 4 Hz, H-1); mass spectrum m/e 207 (M)$^+$, 208 ($M + 1$)$^+$.

Tetrahydropyranyl Ether (21). The tricyclic alcohol (10) (0.75 g) was dissolved in dry benzene. Dihydropyran (0.56 mL) and trifluoracetic acid (0.26 mL) were added and the solution was left at room temperature for 18 h. The benzene solution was washed with saturated aqueous sodium bicarbonate and water and dried ($MgSO_4$) and the solvent was removed under vacuum. Chromatography on silica gel in 1% methanol in chloroform gave the tetrahydropyranyl derivative (0.9 g, 93%) characterized as a diastereoisomeric mixture: $[\alpha]^{26}_D$ −39.2°; 100 MHz NMR ($CDCl$) δ 1.32 (s, 3 H, CH_3), 1.58 (s, 3 H, CH_3), 2.36, 2.38 (2 s, 3 H, NCH_3, rotamers), 3.01, 3.04 (2 s, 1 H, H-3, rotamers), 4.65 (m, 2 H, H-2 and OCHO), 6.04 (2 d, 1 H, J = 5 Hz, H-1). Anal. Calcd for $C_{16}H_{27}NO_6 \cdot \frac{1}{2}H_2O$: C, 56.8; H, 8.3; N, 4.1. Found: C, 57.0; H, 85; N, 3.9.

4-Hydroxymethyl-5-*O*-tetrahydropyranyl-1,2-isopropylidene-3-*N*-formyl-3-*N*-methyl-3-amino-3-deoxy-α,D-arabinofuranoside (22). The tetrahydropyranyl ether 21 (2.7 g) in 25% aqueous methanol was treated with sodium acetate (anhydrous) (4.0 g) and iodine (2.0 g). After 17 h at room temperature, the reaction mixture was partitioned between chloroform and saturated sodium thiosulfate solution. The chloroform layer was washed with water, dried over $MgSO_4$, and evaporated to dryness, to give essentially pure title compound as a gum (91%): $[\alpha]^{26}_D$ −10.6°; NMR ($CDCl_3$) δ 1.2 (s, 3 H, CH_3); 1.6 (m, 12 H, CH_3 and CH_2), 2.93, 3.06 (2 s, 3 H, NCH_3, rotamers), 5.0 (m, 1 H, H-2, rotamers), 6.08 (m, 1 H, H-1); mass spectrum m/e 330 ($M - 15$)$^+$. Anal. Calcd for $C_{16}H_{27}NO_7$: C, 55.6; H, 7.8; N, 4.0. Found: C, 55.4; H, 7.9; N, 3.8.

Reaction of Phynyl Isocyanate with Tricyclic Alcohol (10). Tricyclic alcohol 10 (1 g) and phenyl isocyanate (0.50 g) were dissolved in pyridine (10 mL) and left at room temperature for 18 h. The solvent was removed under high vacuum and the residue was chromatographed on silica gel to give compound 24 as a gum (1.35 g, 92%): $[\alpha]^{26}_D$ −28° (0.4, ethanol); NMR ($CDCl_3$) δ 1.3 (s, 3 H, CCH_3), 1.58 (s, 3 H, CCH_3), 2.35 (s, 3 H, NCH_3), 2.87 (broad singlet, 1 H, H-3), 4.64 (d, 1 H, J = 4.5 Hz, H-2), 6.05 (d, 1 H, J = 4.5 Hz, H-1), 7.35 (m, 5 H, Ar); mass spectrum m/e 364 (M)$^+$, 349 ($M - 15$)$^+$. Anal. Calcd for $C_{18}H_{24}N_2O_6$: C, 59.4; H, 6.6; N, 7.7. Found: C, 59.7; H, 6.8; N, 7.5.

4-Hydroxymethyl-5-*O*-phenylcarbamoyl-1,2-isopropylidene-3-*N*-formyl-3-*N*-methyl-3-amino-3-deoxy-β-L-arabinofuranose (25). The phenylurethane 24 (5.0 g) was dissolved in 25% water in methanol (160 mL) and treated with sodium acetate (10 g) and iodine (10 g). After 2.5 h a further 5 g of each inorganic reagent was added. After a further 30 min, the whole was poured into water (300 mL) and extracted with ethyl acetate (2 × 250 mL). The organic layer was washed with an aqueous solution of sodium thiosulfate and water and dried. The whole was concentrated to dryness and the residue was crystallized from a chloroform–hexane mixture (86%): mp 175–176 °C; $[\alpha]^{26}_D$ −34.90° (0.5, ethanol); NMR ($CDCl_3$) δ 1.33 (s, 3 H, CCH_3), 1.63 (s, 3 H, CH_3), 2.9, 3.04 (2 s, 3 H, NCH_3, rotamers), 4.88, 5.1 (two broad doublets, 1 H, H-2, rotamers), 6.05, 6.16 (2 broad doublets, 1 H, H-1, rotamers), 8.1 (2 s, 1 H, CHO, rotamers); mass spectrum m/e 380 (M^+). Anal Calcd for $C_{18}H_{24}N_2O_7 \cdot \frac{1}{2}H_2O$: C, 55.5; H, 6.4; N, 7.2. Found: C, 55.6; H, 6.25; N, 7.03.

4-Iodomethyl-5-*O*-phenylcarbamoyl-1,2-isopropylidene-3-*N*-formyl-3-*N*-methyl-3-deoxy-α-D-arabinofuranoside (26). The phenylcarbamoyl derivative 25 (2 g) in dry DMF (25 mL) was heated at 80 °C for 18 h with triphenylphosphite methiodide (8.0 g). The cooled reaction mixture was poured in 1 N aqueous potassium hydroxide and extracted with chloroform. The extracts were washed with water, dried, and concentrated to leave an oily residue. Chromatography of the residue on silica gel in benzene–ethyl acetate (1:1) gave the title compound (1.1 g, 44%) as an oil: $[\alpha]^{26}_D$ −20.3°c (0.5, ethanol); NMR ($CDCl_3$) 1.3 (s, 3 H, CCH_3), 1.65 (s, 3 H, CCH_3), 2.9, 3.05 (2 s, 3 H, NCH_3, rotamers), 3.3 (m, 2 H, CH_2I), 5.0 (2 d, 1 H, J = 4 Hz, H-2, rotamers), 6.1 (2 d, 1 H, J = 4 Hz, rotamers), 8.10, 8.16 (2 s, 1 H, rotamers, CHO); mass spectrum m/e 490 (M^+). Anal. Cald for $C_{18}H_{23}N_2O_6I$: C, 44.1; H, 4.7. Found: C, 44.4; H, 4.9.

5-*O*-Phenylcarbamoyl-1,2,isopropylidene-4-*C*-methyl-3-*N*-methyl-amino-3-*N*-formyl-3-deoxy-β-L-arabinofuranoside (27). The iodo derivative 26 (1.0 g) was dissolved in dry benzene (10 mL) and heated at reflux with tri-*n*-butylstannane (1.2 mL) for 6 h. The solvent was removed by evaporation under high vacuum to give an oily residue which was triturated with petroleum ether and the residue was chromatographed on silica gel in benzene–ethyl acetate (1:1) to give the title compound (0.63 g, 85%): $[\alpha]^{26}_D$ −35.4° (0.5, ethanol); NMR ($CDCl_3$) 1.3 (s, 3 H, CCH_3), 1.35 (s, 3 H, CCH_3), 1.66 (s, 3 H, CCH_3), 2.90, 2.98 (2 s, 3 H, NCH_3, rotamers), 4.9 (m, 1 H, H-2, rotamers), 6.0 (t, 1 H, H-1, rotamers), 8.1 (broad singlet, 1 H, CHO); mass spectrum m/e 364 (M^+). Anal. Calcd for $C_{18}H_{24}N_2O_6 \cdot \frac{1}{2}H_2O$: C, 57.9; H, 6.7; N, 7.5. Found: 58.1; H, 6.7; N, 7.1.

Methyl Garosaminides (1). The phenylcarbamoyl derivative (0.5 g) was heated under reflux with 10% hydrazine hydrate in ethanol for 5 h. The solvent and excess hydrazine hydrate were removed by evaporation under high vacuum. The residue was taken up in 6 N methanolic hydrochloric acid and heated at reflux for 3 h. Evaporation of the solvent and chromatography of the residue on silica gel in the lower phase of a chloroform–methanol–7% ammonium hyroxide (2:1:1) solvent system gave methyl garosaminide as an anomeric mixture (0.21 g) (80%) identical in all respects with authentic material.

Garosamine Hydrochloride. The synthetic methyl garosaminide anomeric mixture was heated for 2 h in 6 N aqueous hydrochloric acid.

Evaporation of the solvent gave garosamine hydrochloride identical with authentic material.

Acknowledgments. We thank our colleagues for helpful discussions and Messrs. J. Morton, J. McGlotten, and P. Bartner for spectral data.

Registry No.—**4,** 65483-48-9; **8,** 65483-49-0; **9,** 65483-50-3; **10,** 65483-51-4; **13,** 65483-52-5; **14,** 65483-53-6; **15,** 65483-54-7; **19,** 65483-55-8; **21,** 65483-56-9; **22,** 65483-57-0; **24,** 65483-58-1; **25,** 65483-59-2; **26,** 65483-60-5; **27,** 65504-54-3; garosamine, 29914-71-4; *N*-acetyl-3-amino-3-deoxy-1,2:5,6-diisopropylidine-α-D-galactofuranose, 19131-09-0.

References and Notes

(1) W. Meyer zu Reckendorf and E. Bischof, *Chem Ber.*, **105,** 2546 (1972).
(2) D. J. Cooper, P. J. L. Daniels, M. D. Yudis, H. M. Marigliano, R. D. Guthrie, and S. T. K. Bukhari, *J. Chem. Soc.*, 3126 (1971).
(3) J. J. Wright, P. J. L. Daniels, and A. K. Mallams, *Chem. Commun.*, 676 (1973).
(4) R. Schaffer, *J. Am. Chem. Soc.*, **81,** 5452 (1959).
(5) W. Meyer zu Reckendorf, "Methods in Carbohydrate Chemistry", Vol. 6, R. L. Whistler and J. N. BeMiller, Ed., Academic Press, New York, N.Y., 1972, p 129.
(6) J. S. Brimacombe, P. A. Gent, and M. Stacey, *J. Chem. Soc.*, 567 (1968).
(7) R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLaughlan, *J. Chem. Soc.*, 3699 (1962).
(8) S. Umezawa, T. Tsuchiya, and K. Tatsuta, *Bull. Chem. Soc. J.*, **39,** 1235 (1966).
(9) S. T. Bukari, R. D. Guthrie, A. I. Scott, and A. D. Wrixon, *Tetrahedron*, **26,** 3653 (1970).
(10) J. J. Wright, unpublished observations.

Poly(iminomethylenes). 6.[1] Synthesis and Polymerization of α- and β-D-Glucopyranosyl Isocyanide

Roeland J. M. Nolte, Jean A. J. van Zomeren, and Jan W. Zwikker*

Department of Organic Chemistry of the University, Croesestraat 79, Utrecht, The Netherlands

Received September 6, 1977

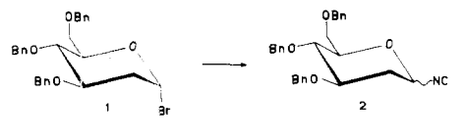
Both anomers of 2,3,4,6-tetra-*O*-benzoyl-D-glucopyranosyl isocyanide have been synthesized starting from 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide. This bromide was converted into the β-azide which after hydrogenation to the amine and formylation afforded *N*-formyl-2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosylamine. Dehydration of the latter compound gave the isocyanides in an α to β ratio of 1:9. Polymerization of the isocyanides was performed with nickel chloride. From the optical rotations it was concluded that the helical polymers obtained from the anomeric monomers are opposites in a screw sense.

Poly(isocyanides), more systematically named poly(iminomethylenes), $[RN{=}C<]_n$, are rigid rod polymers[2] with a helical configuration.[3,4] In general, they are easily prepared from the monomeric isocyanides, RN=C, with nickel chloride or a nickel(II) complex as catalyst.[5,6] Stereoselective formation of either a right-handed (*P*) or left-handed (*M*) helix can be expected when the monomeric isocyanide is one enantiomer of R*N=C, in which R* is chiral.

Because of their ready availability and optical purity natural compounds often are the starting materials of choice for stereoselective syntheses. Our first entry into this field was the synthesis of a poly(iminomethylene) derived from L-histidine.[1] In the present paper we wish to report the synthesis of such polymers derived from glucose. An additional motive for the synthesis of these compounds is the fact that polymer-bounded sugars[7] and especially sugar residues linked to polymer-bounded amino acids may be interesting models in immunological studies.[8]

Results and Discussion

Reaction of silver cyanide with benzyl protected glucopyranosyl halides (1) was recently reported[9] to give formerly unknown isocyano sugars (2).



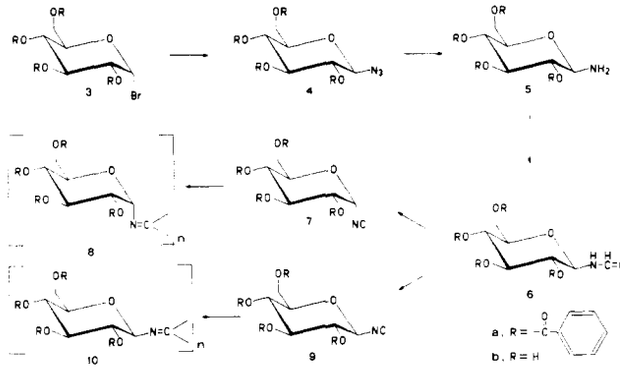
1 2

In our hands, however, this reaction afforded unseparable mixtures of α and β anomers and other unidentified products.

We have synthesized the α and β anomers of D-glucopyranosyl isocyanide, compounds **7** and **9,** via amine **5** and N-substituted formamide **6** according to Scheme I.

A convenient route for the synthesis of per-*O*-acylglycosylamines is provided by the reduction of the corresponding *O*-acylglycosyl azides.[10] Sproviero[11] synthesized 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl azide (**4a**) in 66% yield from 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (**3a**) by a nucleophilic displacement reaction with sodium azide in boiling acetonitrile. We have carried out this reaction by using phase-transfer catalysis in a mixture of chloroform and water. Compound **4a** was isolated in quantitative yield; its β-D-gluco configuration was confirmed by the ^{1}H-NMR spectrum, in which the signal for the anomeric proton appeared as a doublet at 4.95 ppm ($J_{1,2}$ = 8.7 Hz).

Scheme I



Catalytic hydrogenation of the glycosyl azide **4a** over palladium on carbon afforded 1,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosylamine (**5a**) as a white foam. The latter amine was converted into its debenzoylated form (**5b**) by reaction with sodium methanolate in methanol. The infrared absorption spectrum of **5b** showed that this compound was uncontaminated by *N*-benzoylglucopyranosylamine,[12] proving that in the reduction step no O → N benzoyl migration had oc-

0022-3263/78/1943-1972$01.00/0