after 3 h. Similar results were obtained when the latter experiment was repeated without the presence of K_2CO_3.

A solution of the major diastereomer in perchloroethene was heated to 80 °C. No change was observed in the NMR spectrum. At higher temperatures, decomposition to unidentified products occurred.

4-Aza-5-hydroxypregnane-3,6,20-trione (6a). MCPBA (480 mg, 2.79 mmol) was added to a solution of **9a** (376 mg, 0.80 mmol) in 5 mL of chloroform. After 20 min, the reaction mixture was diluted to 20 mL and washed several times with 5% K_2CO_3 solution, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. Crystallization of the residue from chloroform–methanol afforded 201 mg (72%) of carbinol amide **6a** (mp 234–236 °C), having an IR spectrum identical with that of the authentic sample obtained from the oxidation of **5a** with 1.

4-Aza-5,17β-dihydroxyandrostane-3,6-dione (6b). MCPBA (258 mg, 1.50 mmol) was added to a solution of **9b** (208 mg, 0.47 mmol) in 10 mL of chloroform. Workup as in the preceding procedure, followed by crystallization from acetone–hexane, furnished 94 mg (62%) of carbinol amide **6b**: mp 239–242 °C; IR (Nujol) 3440 (OH), 3280 (NH), 1735 (C=O, C-6), 1640 (C=O, C-3) cm^{-1}; ^1H NMR (pyridine-d_5) 3.92 (t, J = 8.4 Hz, 1 H, H-17), 3.0–0.8 (complex, s at 0.96, 0.88, total 24 H); mass spectrum, m/e (relative intensity) 321 (<1, M^+), 303 (13, $M^+ - H_2O$). Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.40; H, 8.65; N, 4.28.

4-Aza-6-hydroxy-5-methoxypregnane-3,20-dione (18). A solution of MCPBA (189 mg, 1.10 mmol) in 10 mL of dichloromethane was added over 30 min to enamide **5a** (315 mg, 1.00 mmol) in 5 mL of dichloromethane and 5 mL of methanol. The reaction mixture was washed three times with 5% $NaHCO_3$ solution, dried over anhydrous $MgSO_4$, and evaporated in vacuo. Crystallization of the product from dichloromethane–ether afforded 152 mg (42%) of **18**, mp 170–172 °C; IR ($CHCl_3$) 3560 (OH), 3380 (NH), 1699 (C=O, C-20), 1668 (C=O, C-3) cm^{-1}; ^1H NMR (200 MHz) 7.00 (br s, exchanged, 1 H, NH), 3.85 (m, 1 H, H-6), 3.26 (s, 3 H, OMe), 2.6–1.0 (complex, s at 2.12, 1.16, total 25 H), 0.64 (s, 3 H, Me); ^{13}C NMR 209.3 (C-20), 174.4 (C-3), 87.4 (C-5), 68.1 (C-6); mass spectrum, m/e (relative intensity) 363 (<1, M^+), 332 (100, $M^+ - OMe$). Anal. Calcd for $C_{21}H_{33}NO_4$: C, 69.39; H, 9.15; N, 3.85. Found: C, 68.58; H, 9.08; N, 3.96. Attempts at further purification resulted in decomposition.

4-Azapregnane-3,6,20-trione (19). The preceding reaction was repeated with 95 mg (0.55 mmol) of MCPBA and 158 mg (0.50 mmol) of **5a**. The reaction mixture was allowed to stand for 24 h prior to workup in the previous manner. Crystallization of the product from dichloromethane–ether provided 93 mg (56%) of **19**: mp 185–210 °C; IR ($CHCl_3$) 3390 (NH), 1720 (C=O, C-6), 1700 (C=O, C-20), 1663 (C=O, C-3) cm^{-1}; ^1H NMR (200 MHz) 6.43 (br s, exchanged, 1 H, NH), 3.85 (s, 1 H, H-5), 2.7–1.0 (complex, s at 2.14, total 21 H), 0.82 (s, 3 H, Me), 0.66 (s, 3 H, Me);[36] ^{13}C NMR 208.8 (C-20), 203.5 (C-6), 170.7 (C-3), 67.5 (C-5); mass spectrum, m/e 331 (M^+). Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.19; H, 8.61; N, 4.36.

Registry No. 1, 17697-12-0; 2, 6996-92-5; **3a**, 57-83-0; **3b**, 58-22-0; **4a**, 3510-20-1; **4b**, 1759-35-9; **5a**, 20283-95-8; **5b**, 82093-09-2; **6a**, 74214-10-1; **6b**, 82093-10-5; **7a**, 74214-11-2; **7b**, 82093-11-6; **8a**, 74214-12-3; **8b**, 82093-12-7; **9a**, 74214-13-4; **9b**, 82093-13-8; **10**, 82093-14-9; 11, 82093-15-0; **12a** (isomer 1), 74214-14-5; 12a (isomer 2), 74214-15-6; **18**, 82093-16-1; **19**, 82093-17-2.

(36) Signals at δ 0.80 and 0.63 (<10% of those at δ 0.82 and 0.66) suggest the presence of an impurity. It is possible that **19** is formed as a mixture of 5α and 5β isomers. This would also account for the broad melting point which was not improved by repeated recrystallization.

Synthesis of Enantiomerically Pure Forms of *N*-Acyl Derivatives of *C*-Methyl Analogues of the Aminodeoxy Sugar L-Acosamine from Noncarbohydrate Precursors

Giovanni Fronza, Claudio Fuganti,* Piero Grasselli, Luisella Majori, Giuseppe Pedrocchi-Fantoni, and Franca Spreafico

Istituto di Chimica del Politecnico, Centro del CNR per la Chimica delle Sostanze Organiche Naturali, 20133 Milano, Italy

Received December 16, 1981

The 2*S*,3*R* diol **2a** and the 3*R* α-ketol **5b**, prepared in fermenting baker's yeast from cinnamaldehyde and α-methylcinnamaldehyde, are converted into the chiral *N*-trifluoroacetyl deoxy *C*-methyl-branched amino sugars **15b,c** and **19b**. Key intermediates in the synthesis are the C_4 and C_5 chiral aldehydes **9a** and **17a** and the α,β-unsaturated carbonyl compounds **11a** and **18**, which upon threo stereoselective addition of ammonia, eventually give **15b,c** and **19b**. The stereochemistry and the conformations of the aminodeoxy sugar derivatives and of the intermediate lactones are deduced by NMR studies.

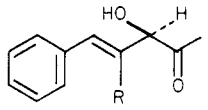
A current approach[1] to the synthesis of enantiomerically pure forms of natural products and drugs is based on the use as starting materials of components of the collection of inexpensive, readily available, optically active compounds produced by nature, called the "pool of chirality", which includes, among others, carbohydrates, amino acids, hydroxy acids like tartaric, malic, lactic, and citramalic, alcohols like D-mannitol, and a few terpenes. Chemists are, however, not fully satisfied with the present composition of the "pool of chirality", since most of the compounds are available in only one enantiomeric form, a circumstance which dictates, when the absolute configuration of the target molecule is opposite the one of the chosen starting material, chemical manipulation of the chiral center(s), usually through multistep, low-yield sequences. This is the case of the synthesis of the 2,3,6-trideoxy-3-aminohexoses of the L series present in the therapeutically important anthracycline glycosides daunomycin (**26a**), adriamycin (**26b**), and their 4′-epimers (**26c** and **26d**),[2]

(1) Seebach, D.; Kalinowski, H.-O. *Nachr. Chem. Tech.* **1976**, *24*, 415.

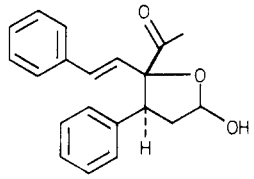
(2) Arcamone, F.; Franceschi, G.; Orezzi, P.; Cassinelli, G.; Barbieri, W.; Mondelli, R. *J. Am. Chem. Soc.* **1964**, *86*, 5334. Arcamone, F.; Cassinelli, G.; Orezzi, P.; Franceschi, G.; Mondelli, R. *Ibid.* **1964**, *86*, 5335. Arcamone, F.; Franceschi, G.; Penco, S.; Selva, A. *Tetrahedron Lett.* **1969**, 1007. Arcamone, F.; Penco, S.; Vigevani, A.; Redaelli, S.; Franchi, G.; Di Marco, A.; Casazza, A. M.; Dasdia, T.; Tormelli, F.; Necco, A.; Soranzo, C. *J. Med. Chem.* **1975**, *18*, 703.

0022-3263/82/1947-3289$01.25/0

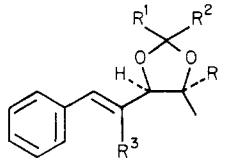
Chart I



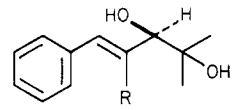
5a, R = H
b, R = Me



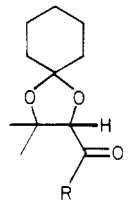
6



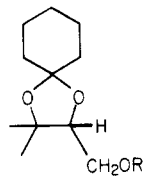
8a, R = H; R^1 = R^2 = Me; R^3 = H
b, R = R^3 = Me; R^1, R^2 = $(CH_2)_5$
c, R = H; R^1 = R^2 = R^3 = Me



7a, R = H
b, R = Me



9a, R = H
b, R = Me
c, R = OH
d, R = OMe

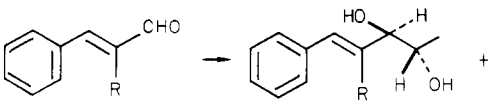


10a, R = H
b, R = $COC(CF_3)(C_6H_5)(OMe)$

which can be realized either from inexpensive hexoses of the D series,[3] but with a critical inversion of configuration at position 5 at some stage of the sequence, or from the rather rare 6-deoxy sugar L-rhamnose.[4]

Accordingly, there is considerable interest in finding new chiral products which can be used as starting materials for syntheses of enantiomerically pure forms of elaborated substances, and a particularly rich source of chiral compounds are expected to be the transformations of nonconventional substrates by microorganisms.[5] Microbes are indeed capable of performing a variety of transformations of nonconventional substrates using enzymes either of the primary or of the secondary metabolism.[6] Furthermore, through suitable technics it is possible to induce in a microorganism an enzymic activity enabling one to transform an added unnatural substrate into definite products. From a practical point of view, we would expect to be synthetically useful those transformations of nonconventional substrates leading to optically active products performed by microorganisms commercially available at low cost, possessing large quantities of enzymes (usually of the primary metabolism), and showing a wide substrate specificity, while maintaining a precise reaction stereospecificity.

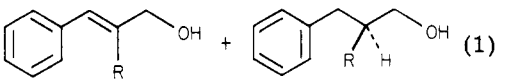
In this context, the baker's yeast mediated conversion[7] of aromatic, α,β-unsaturated aldehydes into the set of products indicated in eq 1 seems particularly interesting. The 2*S*,3*R* diols **2** are expected to arise by reduction of the



1a, R = H
b, R = Me
c, R = Br

2a, R = H
b, R = Me
c, R = Br

15-25%



(1)

3a, R = H
b, R = Me
c, R = Br

20-30%

4a, R = H
b, R = Me
c, R = Br

65-45%

α-ketols **5**,[8a,b] (Chart I) formed by an acyloin-type condensation of a C_2 unit onto the aldehydic carbonyl carbon. Under appropriate experimental conditions,[8a] the α-ketol **5b** has been obtained as the sole transformation product from **1b**, whereas the corresponding compound (**5a**) from cinnamaldehyde does not survive the fermentation conditions, being captured by a molecule of cinnamaldehyde to give a Michael adduct which is eventually cyclized to optically inactive **6**. The relevant structural features of compounds **2** enabled us to use these chiral educts as starting materials in the synthesis of enantiomerically pure forms of natural products belonging to quite different structural classes.

Indeed, from the diols of type **2** we have obtained deoxy- and 3-*C*-methyl-branched deoxy sugars of the L series,[9] D-(−)-allomuscarine,[10] the enantiomeric forms of γ-hexanolide,[11] (+)- and (−)-*exo*- and -*endo*-brevicomin,[12] and, in the field of the deoxyamino sugars, *N*-(trifluoroacetyl)-L-acosamine and -L-daunosamine[13] and the *N*-benzoyl derivative of L-vancosamine and of its configurational isomers.[14]

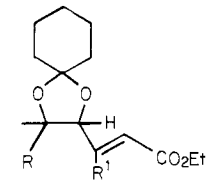
The synthesis of *N*-(trifluoroacetyl)-L-acosamine (**27a**) and L-daunosamine (**27b**) from the easily available diol **2a** appears to be an attractive alternative to ones based on carbohydrates.[3,4] For this reason, in a program designed to obtain enantiomerically pure forms of the *C*-methyl analogues of the above deoxy amino sugars components of the antitumor agents **26** for subsequent testing of the derived glycosides, we decided to use the above set of chiral products prepared from α,β-unsaturated aldehydes and baker's yeast as starting materials, and we refer now on the results of our studies.

Synthesis of *N*-Acyl Derivatives of *C*-Methyl Analogues of L-Acosamine

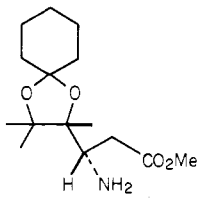
The *N*-acyl derivatives of the 5-*C*-methyl analogue of L-acosamine (**15** and/or **16**, Chart II) seemed available from the aldehyde **9a** through a sequence similar to the one followed in the conversion of **17a** into **27a** and **27b**.[13] The expected intermediates had to be the C_6 α,β-unsatu-

(3) Horton, D.; Weckerle, W. *Carbohydr. Res.* **1976**, *46*, 227.
(4) Marsh, J. P.; Mosher, C. W.; Acton, E. M.; Goodman, L. *Chem. Commun.* **1967**, 973.
(5) Fischli, A. In "Modern Synthetic Methods"; Scheffold, R., Ed.; Salle and Sauerländer: Frankfurt am Main, 1980; Vol 2, p 269.
(6) Jones, J. B.; Sih, C. J.; Perlman, D. "Applications of Biochemical Systems in Organic Chemistry"; Weissberger, A., Ed.; Wiley: New York, 1976; Vol. I, II.
(7) Fuganti, C.; Grasselli, P. *Chem. Ind. (London)* **1977**, 983. Fuganti, C.; Grasselli, P.; Marinoni, G. *Tetrahedron Lett.* **1979**, 1161.
(8) (a) Bertolli, G.; Fronza, G.; Fuganti, C.; Grasselli, P.; Majori, L.; Spreafico, F. *Tetrahedron Lett.* **1981**, 965. (b) Neuberg, C.; Ohle, H. *Biochem. Z.* **1922**, *128*, 610.
(9) Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1978**, 299.
(10) Fronza, G.; Fuganti, C.; Grasselli, P. *Tetrahedron Lett.* **1978**, 3941.
(11) Bernardi, R.; Fuganti, C.; Grasselli, P.; Marinoni, G. *Synthesis* **1980**, 50.
(12) Bernardi, R.; Fuganti, C.; Grasselli, P. *Tetrahedron Lett.* **1981**, 4021.
(13) Fronza, G.; Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1980**, 442.
(14) Fronza, G.; Fuganti, C.; Grasselli, P.; Pedrocchi-Fantoni, G. *Tetrahedron Lett.* **1981**, 5073.

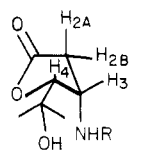
Chart II



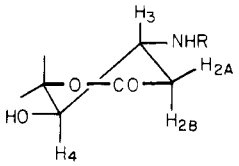
11a, R = Me; R′ = H
b, R = H; R′ = Me



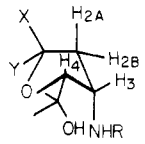
12



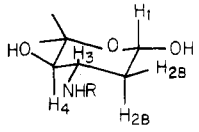
13a, R = COC_6H_5
b, R = $COCF_3$



14, R = $COCF_3$



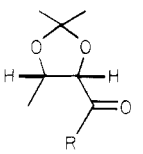
15a, R = COC_6H_5; X, Y = H, OH
b, R = $COCF_3$; X = OH; Y = H
c, R = $COCF_3$; X = H; Y = OH



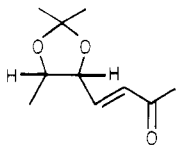
16a, R = COC_6H_5
b, R = $COCF_3$

rated ester **11a**, the β-amino ester **12**, and the lactones **13** and/or **14**, reduced, in turn, to **15** and/or **16**. Exploratory experiments with racemic **9a**, easily prepared from 3-methyl-2-butenoic acid (see Experimental Section), yielded racemic **11a**, which added ammonia stereoselectively to form the threo[13,15] adduct **12**, as shown by its conversion into an *N*-trifluoroacetyl δ-lactone, indicated by NMR studies (see below) to have structural formula **14**, and into the γ isomer **13b**. Diisobutylaluminum hydride reduction of the above lactones yielded the *N*-trifluoroacetyl deoxyamino sugar derivatives **15b,c**. The two lactones **13b** and **14** are obtained in ca. a 10:1 ratio by treating with $(CF_3CO)_2O$ the corresponding lactone hydrochloride, as obtained upon acid treatment of **12**. Kept in solution (MeOH or Me_2SO), the δ-lactone **14** is converted into the γ isomer **13b**. In the N-benzoylated series, we have isolated only the γ-lactone **13a**, at variance with the behavior observed for the *N*-benzoyl lactone corresponding to L-acosamine, where the γ and δ forms were interconvertible.[13] Our initial aim for the preparation of enantiomerically pure forms of **15a** and **15b** was that of using the α-ketol **5a**, which had to be prepared from cinnamaldehyde and baker's yeast. Indeed, **5a** seemed convertible, if obtained, into a compound like **7a**, from which the required (2*S*)-aldehyde **9a** was prepared through well-established procedures. However, the fermentation experiments indicated that **5a**, though formed, does not survive the fermentation conditions, being converted into **6**. We then turned out attention to the 3*R* α-ketol **5b**. This material gave with MeMgI the adduct **7b** (mp 74 °C; $[\alpha]^{20}$ +95°; 90% yield) which was protected by conversion into oily **8b** ($[\alpha]^{20}_D$ −75.5°; 93% yield) and ozonized to give benzaldehyde and the methyl ketone **9b**, in ca. 75% overall yield. The chromatographic separation of the above mixture was quite difficult, and we have been able to obtain the ketone **9b** containing ca. 20% of benzaldehyde. However, the crude material was submitted to haloform degradation to yield the acid **9c**, reduced without purification to the alcohol **10a**. The latter was characterized as the ester with (+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid **10b**, $[\alpha]^{20}_D$ +47.4°. ^1H NMR studies on **10b** and comparison with the ester obtained from the racemic modification of **10a** ($[\alpha]^{20}$ +38.9°) showed it to be enantiomerically pure. The alcohol **10a** was oxidized with pyridinium chlorochromate in CH_2Cl_2, and the reaction mixture containing the aldehyde **9a** and some unreacted **10a** was treated with $(C_6H_5)_3P{=}CHCO_2Et$ to give in ca. 60% yield from **10a** the chiral ester **11a**. The latter material was reacted with a large excess of dry ammonia in methanol for 5 days at room temperature. The evaporated reaction mixture, once hydrolyzed with 2 N HCl, was benzoylated in the presence of K_2CO_3 with C_6H_5COCl to give, after acidification, as the sole reaction product the *N*-benzoyl γ-lactone **13a**: oil; $[\alpha]^{20}_D$ +17.3°; ca. 50% yield (from **11a**). The lactone **13a**, reduced with diisobutylaluminum hydride in tetrahydrofuran, gave in ca. 80% yield the (benzoylamino)deoxy sugar **15a**: mp 65 °C; $[\alpha]^{20}_D$ +22.8° (*c* 0.5, methanol, after 15 min).

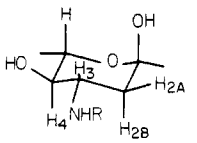
Chart III



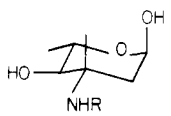
17a, R = H
b, R = Me



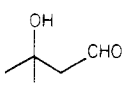
18



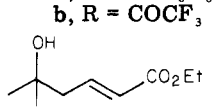
19a, R = COC_6H_5
b, R = $COCF_3$



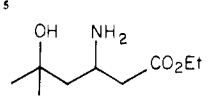
20, R = COC_6H_5



21



22



23

The framework of the 1-*C*-methyl analogue of L-acosamine was obtained from the diol **2a** in a way similar to the one followed in the synthesis of *N*-(trifluoroacetyl)-L-acosamine (**19b**).[13] This route involves as the key intermediate the C_4 chiral aldehyde **17a** (Chart III). In a one-pot sequence, the isopropyliden derivative **8a** (oil; $[\alpha]^{20}_D$ −2.45° (neat)) was treated with (i) O_3 in CH_2Cl_2 solution at −20 °C, (ii) 1 molar equiv of triphenylphosphine to decompose the intermediate ozonide, and (iii) 1.8 molar equiv of $(C_6H_5)_3P{=}CHCOCH_3$ from −20 °C to reflux to give ca. a 70% overall yield of the α,β-unsaturated ketone **18** ($[\alpha]^{20}_D$ +1.7°), separated from benzalacetone by SiO_2 column chromatography. The C_7, unsaturated, chiral ketone **18** was reacted with dry ammonia in methanol at room temperature for 5 days to give, after acid hydrolysis of the addition product, a crystalline hydrochloride, mp 98 °C. The latter material upon N-benzoylation yielded crystalline **19a**: mp 162 °C; $[\alpha]^{20}_D$ −65°; (ca. 55% overall from **18**). The assignment of the arabino stereochemistry depicted in structural formula **19a** is based on NMR studies (see below). Treatment of the above-mentioned hydrochloride with an excess of $(CF_3CO)_2O$ in methylene chloride led to the derivative **19b**. Again, the addition of ammonia across the α,β-unsaturated chiral ketone **18** took place stereoselectively to give the product of threo stereochemistry relative to the newly formed chiral center.

An attempt to prepare the 3-*C*-methyl analogue of L-acosamine from the C_5 chiral methyl ketone **17b**, obtained from **2b** via **8c** and ozonolysis by following the same route

(15) Fronza, G.; Fuganti, C.; Grasselli, P. *Tetrahedron Lett.* **1979**, 3883.

as for the α,β-unsaturated ester **11b**, failed because we have been unable to add ammonia across the trisubstituted double bond of **11b**, even using dry ammonia in methanol for 1 week at 100 °C in a sealed tube. Accordingly, the required *N*-benzoyl derivative of 2,3,6-trideoxy-3-*C*-methyl-3-amino-L-*arabino*-hexose (**20**) has been prepared from the same ketone (**17b**) via the benzenesulfenimine and stereoselective addition of allylmagnesium bromide. This route renders accessible also the L-*lyxo* and L-*xylo* isomers of **20**.[14] However, since the synthetic scheme followed here is conceptually different from that reported above and is based on the stereoselective addition of ammonia to α,β-unsaturated carbonyl compounds bearing a γ-alkoxy chiral center, the full experimental details relative to the synthesis of **20** will be presented when the preparation of the fourth configuration isomer, namely, the L-*ribo* (now in progress), is completed.

We had also intended to carry out the synthesis of the *N*-acyl derivatives of the optically active form of the 4-deoxy-5-*C*-methyl analogue of L-acosamine (**25**, Chart IV). They seemed accessible through deoxygenation at position 4 of suitable intermediates in the synthesis of **15** and **16**. For comparison purposes we synthetized first the racemic modification of **25** starting from the aldehyde **21**, the α,β-unsaturated ester **22**, and the β-amino ester **23**, (see Experimental Section). However, the synthesis of the optically active form of **25** through the above-mentioned route could not be realized, since the intermediates of the synthesis of optically active **15** and **16**, only the δ-lactone **14** incorporates the requisite of having a free hydroxyl group at position 4, but **14** is only a minor product in the sequence. The synthesis of racemic **25** and the NMR data of the intermediate lactone **24** and of the *N*-acyl deoxy sugar **25** are here reported only as matter of record.

Discussion of the NMR Spectra

The discussion of the NMR spectra is limited to the *N*-trifluoroacetyl derivatives of the above-mentioned lactones and of the amino sugars, since they are the most important from a synthetic point of view. The two isomeric lactones, namely, the γ-lactone **13b** and the δ-lactone **14**, were distinguished by the chemical shifts of the carbonyl carbon at position 1, since C-1 is shifted upfield by ca. 5 ppm in a six-membered ring with respect to the five-membered structure[16] (Table IV). The stereochemistry of the δ-lactone **14** can be determined from the values of the vicinal coupling constants (Table I), provided that the conformation of the lactone ring is known. The value of 18.5 Hz for J_{gem} strongly supports[17-19] the half-chair conformation for compound **14**. In this structure the vicinal coupling constants, particularly $^3J(3,4)$ = 10.2 Hz, are consistent with trans diequatorial orientation (threo configuration) of the two substituents NHR and OH.

The vicinal coupling constants have been widely used for the determination of the conformation of γ-lactones.[20] For this purposes the $^3J(3,2B)$ (1.8 Hz) in the γ-lactone **13b** is particularly revealing, since such a small coupling is typical for vicinal trans pseudoequatorial hydrogens.[20] Thus, **13b** exists in the envelop conformation E_3 (or in the very similar twist conformation $^4T_3$) with a quasi-equatorial orientation of the bulky substituent C(OH)Me_2 and a

Table I. ^{1}H NMR Data of the 5-*C*-Methyl Derivatives 13-16[a]

compd	chemical shift						coupling constant				
	H-1	H-2A	H-2B	H-3	H-4	Me-5	J(1,2A)	J(1,2B)	J(2A,2B)	J(3,2A)	J(3,2B)	J(3,4)
13b[b]		3.00	2.76	4.70	4.34	1.34			18.1	5.6	1.8	5.0
14[c]		3.09	2.62	4.30	3.75	1.39			18.5	7.5	9.3	10.2
15b[b]	5.68	2.27	2.46	4.41	3.97	1.26[d]	4.0	5.5	14.7	6.5	1.6	4.3
15c[b]	5.62	~2.24	~2.24	4.56	3.86	1.27[d]	4.0	1.3	*e*	*e*	*e*	5.4
16b[f]	4.89	1.88	1.50	3.90	3.25	1.13	2.6	9.6	12.4	4.8	12.4	10.3

[a] Chemical shifts are in parts per million from internal Me_4Si. Coupling constants are in hertz. [b] Solvent $CDCl_3$. [c] Solvent $CDCl_3$ + Me_2SO (50%). [d] Assignments may be interchanged. [e] Not determined. [f] Solvent Me_2SO + D_2O.

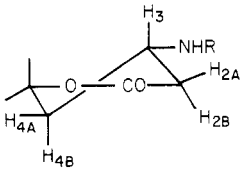
(16) Stothers, J. B., "Carbon-13 NMR Spectroscopy"; Academic Press: New York, 1972; p 300.
(17) Carroll, F. I.; Blackwell, J. T. *Tetrahedron Lett.* **1970**, 4173.
(18) Barfield, M.; Grant, D. M. *J. Am. Chem. Soc.* **1963**, *85*, 1899.
(19) Äyras, P.; Pihlaja, K. *Tetrahedron* **1973**, *29*, 1311.
(20) Johnson, R. N.; Lowry, J. B.; Riggs, N. V. *Tetrahedron Lett.* **1967**, 5113.

Table II. ^{1}H NMR Data of the 1-*C*-Methyl Derivative **19b**[a]

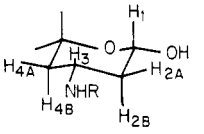
H-2A	H-2B	H-3	H-4	H-5	Me-5	Me-1	OH-4	OH-1	NH
(*J*(2A,2B))	(*J*(3,2A))	(*J*(3,2B))	(*J*(3,4))	(*J*(4,5))	(*J*(5,Me))	(*J*(3,NH))	(*J*(4,OH-4))	(*J*(2B,OH-1))	
1.81	1.55	4.08	3.03	3.76	1.13	1.29	4.90	5.70	9.06
(12.5)	(5.0)	(12.0)	(9.5)	(9.5)	(6.3)	(8.0)	(6.0)	(1.5)	

[a] Chemical shifts are in parts per million from internal Me_4Si. Coupling constants are given in hertz in parentheses. The solvent was Me_2SO.

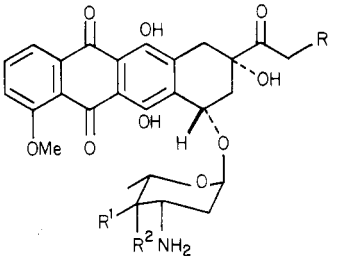
Chart IV



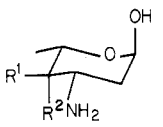
24, R = $COCF_3$



25, R = $COCF_3$



26a, R = R^1 = H; R^2 = OH
b, R = R^2 = OH; R^1 = H
c, R = R^2 = H; R^1 = OH
d, R = R^1 = OH; R^2 = H



27a, R^1 = H; R^2 = OH
b, R^1 = OH; R^2 = H

quasi-axial orientation of the (trifluoroacetyl)amino group.

The reduction of both the lactones **13b** and **14** afforded the same deoxyamino sugar derivatives (**15b,c**) and/or **16** which show a tautomeric composition strongly dependent upon the solvent. It exists almost exclusively as a mixture of α-(**15b**) and β-furanose (**15c**) tautomers in chloroform in about a 1:1 ratio; by addition of D_2O to the chlorofom solution the equilibrium is shifted toward the β-pyranose form (**16b**, ca. 50%). In Me_2SO the β-pyranose structure becomes preponderant, reaching 70% of the tautomeric mixture (α-pyranose isomer, 15%). It is known that the furanose/pyranose ratio is affected by differences in the extent of solvation.[21] In polar solvents the hydroxyl groups are solvated by forming intermolecular hydrogen bonds with the solvent molecules. Most probably, in the less polar solvent chloroform the intermolecular interactions can be replaced by intramolecular hydrogen bonds, thus stabilizing the five-membered-ring structure.

As shown in Table I, only the ^{1}H spectra of the α-furanose (**15b**) and β-pyranose (**16b**) could be fully analyzed, whereas partial NMR data are reported for the β-furanose tautomer (**15c**). The inspection of the vicinal coupling constants of **16b** confirms the trans diequatorial position of the OH at C-4 and of the $NHCOCF_3$ substituents (threo configuration) previously deduced for the δ-lactone precursor and reveals that **16b** is stable in the $^1C_4$ (L) conformation.[22] Analogously to the γ-lactones, the ring vicinal coupling constants can be used to predict the predominant conformation of a furanose ring.[23] The value of 1.6 Hz for ^3J(3,2B) in **15b** can be associated with a dihedral angle of 80–90° between the two trans hydrogens H-2B and H-3, and ^3J(1,2A) corresponds most probably to the angle of 120–130° between H-1 and H-2A. Therefore, the favored conformation of **15b** is E_3 (or $^4T_3$), showing a pseudoaxial and a pseudoequatorial orientation of the two substituents $NHCOCF_3$ and $C(OH)Me_2$, respectively, while OH-1 does not have a definite "axial" or "equatorial" character.

The ^{1}H chemical shifts and coupling constants of **19b** are collected in Table II. Once again the threo stereochemistry at the chiral centers C-3 and C-4 and the $^1C_4$ (L) ring conformation at apparent from the vicinal coupling constants. Compound **19b** gives rise to one single tautomeric species with the anomeric hydroxyl group in the axial position. The stereochemistry at C-1 was established on the basis of the ^{13}C chemical shift of Me-1 (27.8 ppm, Table IV), which indicates an equatorially oriented methyl group (axial methyl groups are expected to resonate at ca. 23 ppm; see, for example compound **25** in Table IV). This assignment was substantiated by the observation of a four-bond coupling constant of 1.5 Hz between OH-1 and H-2B. This long-range coupling is generally observed in sugars provided that the hydroxyl group and the hydrogen atom are axial.[24,25]

The ^{1}H NMR data of the δ-lactone **24** and of the related amino sugar **25** are reported in Table III. The value of 18.1 Hz for ^2J(2A,2B) suggests that **24** adopts the half-chair conformation, which is confirmed also by the existence of a long-range coupling of 1.6 Hz between the H-2A and H-4A protons. These protons, in the half-chair conformation, are in the planar W configuration necessary for observation of this long-range interaction. The values of the vicinal coupling constants are consistent with the equatorial position of the $NHCOCF_3$ group both in the δ-lactone **24** and in the amino sugar **25** ($^1C_4$ (L) conformation). Here too the β-pyranose form **25** is preponderant in solution, reaching 75% of the tautomeric mixture. Clearly, the α anomer is unfavored, owing to the interaction between the axial oxygen atom and the axial methyl group (2.5 kcal/mol).[21]

Conclusions

The work above thus shows the obtainment of enantiomerically pure forms of *N*-acyl derivatives of *C*-methyl analogues of the biologically important aminodeoxy sugar L-acosamine from compounds **2a** and **5b**, belonging to the class of chiral products prepared from baker's yeast and nonconventional substrates. This result gives further support to the synthetic significance of these chiral C_6–C_5 educts obtained from C_6–C_3 aldehydes. Indeed, these compounds not only serve as valid alternatives to natural carbohydrates in the synthesis of natural deoxyamino sugars of the L series, but can also be conveniently used as starting materials in the synthesis of C-methylated unnatural analogues. Furthermore, the C_4 and C_5 chiral carbonyl compounds embodying α(and β)-alkoxy moieties, key intermediates in the above syntheses, can be used as

(21) Angyal, S. J. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 157.
(22) Altona, C.; Haasnot, C. A. G. *Org. Magn. Reson.* **1980**, *13*, 417.
(23) Hall, L. D.; Steiner, P. R.; Pedersen, C. *Can. J. Chem.* **1970**, *48*, 1155. Stevens, J. D.; Fletcher, G. H. *J. Org. Chem.* **1968**, *33*, 1799.
(24) Fronza, G.; Fuganti, C.; Grasselli, P. *J. Chem. Soc., Perkin Trans 1* **1982**, 885.
(25) Gillet, B.; Nicole, D.; Delpuech, J.; Gross, B. *Org. Magn. Reson.* **1981**, *17*, 28.

Table III. ^{1}H NMR Data of the 4-Deoxy-5-*C*-methyl Derivatives 24 and 25[a]

compd	chemical shift							coupling constant						
	H-1	H-2A	H-2B	H-3	H-4A	H-4B	Me-5	Me-5	J(1,2A)	J(1,2B)	J(2A,2B)	J(3,2A)	J(3,2B)	J(3,4A)	J(3,4B)	J(4A,4B)	J(4A,2A)
24		3.02	2.43	4.50	2.20	1.81	1.47	1.49			18.1	6.6	10.2	4.7	12.3	13.3	1.6
25	5.11	2.25	1.30	4.27	1.88	1.43	1.29	1.35	2.5	8.8	12.4	4.1	11.5	4.4	12.1[b]	13.0	1.5

[a] Chemical shifts are in parts per million from internal Me_4Si. Coupling constants are in hertz. The solvent was $CDCl_3$. [b] Taken from Me_2SO solution.

starting materials in the preparation of optically active elaborated natural products by taking advantage of the known methods for acyclic stereocontrol in the chain elongation.

Experimental Section[29]

(3*R*)-3-Hydroxy-4-methyl-5-phenyl-4-penten-2-one (5b). In a 30-L glass jar a mixture is made up composed of 2.5 kg of commercial baker's yeast, 3.2 kg of sugar beet molasses, 20 g of KH_2PO_4, 10 g of $MgSO_4 \cdot 7H_2O$, and 64 g $(NH_4)_2HPO_4$ in 20 L of tap water at 32 °C. As the fermentazion starts, the pH is adjusted with 10% H_3PO_4 to 5, and, under stirring, 115 g of α-methylcinnamaldehyde (**1b**) and 200 mL of acetaldehyde are added from two dropping funnels. After 4 h at 28–32 °C, 1 kg of Celite is added, the reaction mixture is filtered on a large Büchner funnel, the solid pad is washed with 2 L of ethyl acetate, and the filtrate is extracted twice with 4-L portions of ethyl acetate. The organic phase, once dried (Na_2SO_4), is evaporated, leaving a residue of ca. 100–110 g. A 40-g sample of the above crude extract is chromatographed on 350 g of SiO_2 with hexane as the eluent to give ca. 30 g of unreacted aldehyde and with hexane–ethyl acetate (98:2 to 90:10) to give a mixture of **3b** and **5b** and, eventually, ca. 7 g of **5b**: yellowish oil; $[\alpha]^{20}_D$ −412° (*c* 1, $CHCl_3$). The yield of **5b** from **1b** varies from 10% to 20%. An analytical sample is obtained by bulb-to-bulb distillation [oven temperature 80 °C (0.1 mmHg)]: ^{1}H NMR ($CDCl_3$) δ 4.06 (OH), 6.70 (H-5), 4.65 (H-3), 2.19 (CH_3CO), 2.71 (C-3 CH_3). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.55; H, 7.38.

(3*R*)-2,4-Dimethyl-5-phenyl-4-pentene-2,3-diol (7b). To a stirred solution of MeMgI (prepared from 11.5 g (0.5 mol) of Mg) in 350 mL of Et_2O at −10 °C with stirring and in the presence of N_2 is added dropwise 19 g (0.1 mol) of the α-ketol **5b** in 60 mL of Et_2O. After being stirred for a further 3 h, the reaction mixture is treated with 100 mL of a saturated solution of NH_4Cl in water. The separated organic phase is washed with water (2 × 100 mL) and dried (Na_2SO_4) to give upon evaporation of the solvent a solid residue. This material separated from boiling ethyl acetate–hexane as crystalline **7b**: mp 74 °C; $[\alpha]^{20}_D$ +95° (*c* 0.5, MeOH); 16 g (80%); ^{1}H NMR ($CDCl_3$) δ 2.37 (OH), 6.49 (H-5), 3.98 (H-3), 1.83 (C-4 CH_3), 1.30 and 1.22 (2 s, 2 CH_3). Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.76; H, 8.87.

Cyclohexylidene Derivative of (3*R*)-2,4-Dimethyl-5-phenyl-4-pentene-2,3-diol (8b). A mixture of 16 g (0.077 mol) of **7b**, 15 g (0.158 mol) of cyclohexanone, and 0.2 g of 4-toluenesulfonic acid in 0.5 L of benzene is slowly distilled until the separation of water in the distillate is completed. The organic phase is washed with 50 mL of a saturated solution of $NaHCO_3$, dried (Na_2SO_4), and evaporated under vacuum. The yellowish oily residue is chromatographed on 200 g of SiO_2 with hexane to give **8b**: (93%); oil; $[\alpha]^{20}_D$ −75.5° (*c* 0.5, MeOH). A bulb-to-bulb distillation at 120 °C (oven, 1 mmHg) yields an analytical sample: ^{1}H NMR ($CDCl_3$) δ 6.7 (H-5), 4.30 (H-3), 1.9 (C-4 CH_3), 1.10 and 1.42 (2 s, 2 CH_3). Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.81; H, 9.10.

Cyclohexylidene Derivative of (3*S*)-4-Methyl-3,4-dihydroxypentan-2-one (9b). Ozonized oxygen is passed through a solution of 20 g (0.07 mol) of **8b** in 250 mL of dry CH_2Cl_2 at −25 to +20 °C until the consumption of ozone is ended. N_2 is fluxed for 10 min, and, at the same temperature with stirring, 18.5 g of $(C_6H_5)_3P$ is added portionwise. After the reaction mixture is kept at room temperature for 1 h, the reaction mixture is concentrated under vacuum to half its volume and poured into 500 mL of petroleum ether (bp 35–55 °C), and the precipitated $(C_6H_5)_3PO$ is filtered off. The solvent is evaporated at reduced pressure, and the oily residue is chromatographed on a column with 300 g of SiO_2 with hexane–ethyl acetate to give ca. 10 g (75%) of a mixture containing the ketone **9b** along with ca. 20% benzaldehyde (by GLC and NMR). The mixture showed the following: $[\alpha]^{20}_D$ +3.2° (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.10 (H-3), 2.30 (CH_3CO), 1.42 and 1.10 (2 s, 2 CH_3).

2,3-Cyclohexylidene Derivative of (2*R*)-3-Methyl-1,2,3-butanetriol (10a). To a solution of the above mixture (6 g) containing ca. 80% **9b** (0.023 mol) in 330 mL of dioxane and 10 mL of water is added dropwise under stirring at 0 °C and a solution of NaOBr[26] obtained from 12.8 g of NaOH, 113 mL of

Table IV. ^{13}C Chemical Shifts of the Reported Lactones and Amino Sugars[a]

compd	chemical shift							
	C-1	C-2	C-3	C-4	C-5	Me-5	Me-5	Me-1
13b	174.7	37.6	50.2	83.6	71.7	23.8	28.8	
14[b]	168.4	34.9	47.0	72.0	82.8	21.8 (ax)	27.4 (eq)	
15b[c]	97.2	40.9	50.8	85.4	71.8	29.5	24.4	
15c[c]	97.5	41.9	53.1	81.3	71.4	29.5	23.8	
16b[d]	88.3	38.4	48.5	73.9	74.8	17.7 (ax)	28.5 (eq)	
19b[d]	94.3	40.6	49.6	72.9	68.8	18.2		28.7 (eq)
24	169.1	35.0	41.7	39.4	81.3	27.3	30.3	
25	89.4	38.5[e]	43.5	40.7[e]	71.5	22.9 (ax)	31.4 (eq)	

[a] Chemical shifts are in parts per million from internal Me_4Si. The solvent was $CDCl_3$ except otherwise indicated. [b] Solvent $CDCl_3$ + Me_2SO (50%). [c] The signal assignments of **15b** may be interchanged with those of **15c**. [d] Solvent Me_2SO. [e] Assignment may be interchanged.

H_2O, 75 mL of dioxane, and 4.35 mL of Br_2. After the mixture was stirred 3 h at 0 °C, 5 g of Na_2SO_3 in 50 mL of water is added, and the mixture is poured into 140 mL of 10% NaOH. The alkaline solution is extracted with 200 mL of diethyl ether (discarted) and carefully acidified with 2 N HCl in the presence of 300 mL of CH_2Cl_2 at 0 °C. The organic phase, once dried (Na_2SO_4), is evaporated to leave ca. 3.4 g of a thick oily residue containing impure **9c**. The latter mixture, without further purification, dissolved in 20 mL of diethyl ether is added to a boiling mixture of 2 g of $LiAlH_4$ in 200 mL of diethyl ether under N_2. After 2 h under these conditions, 50 mL of a saturated solution of sodium potassium tartrate is added, and the organic phase, once separated, is washed with 50 mL of water, dried (Na_2SO_4), and evaporated to give 2.3 g (ca. 75%) of the alcohol **10a** as an oil showing a negligible optical rotation: ^1H NMR ($CDCl_3$) δ 2.86 (OH), 3.50–4.20 (3 H), m, CH_2OH + H-3), 1.42 and 1.10 (2 s, 2 CH_3). The ester with (+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (**10b**) is prepared[27] from 0.1 g of **10a** and 0.1 mL of acid chloride in 0.5 mL of dry pyridine. After 5 h at room temperature, the reaction mixture is treated with ice–water and extracted with diethyl ether (2 × 20 mL), and the organic phase is evaporated. The residue is purified by preparative TLC ($CHCl_3$) to give **10b**: $[\alpha]^{20}_D$ +47.4° (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.94 (H-2), 4.29 and 4.49 (2 H, H-1, J_{gem} = 11.5 Hz, J_{CH_2CH} = 7.2 and 4.6 Hz), 3.53 (OCH_3), 1.24 and 1.11 (2 s, 2 CH_3). The ester prepared from racemic **10a** showed the following: $[\alpha]^{20}_D$ 38.9 (*c* 0.5, $CHCl_3$); ^1H NMR 3.97 (H-2), 4.19 and 4.57 (2 H, H-1, J_{gem} = 11.5 Hz, J_{CH_2CH} = 7.0 and 4.8 Hz), 3.54 (OCH_3), 1.24 and 1.08 (2 s, 2 CH_3).

2,3-Cyclohexylidene Derivative of Racemic 3-Methyl-1,2,3-butanetriol (10a). 3-Methyl-2-butenoic acid (100 g, 1 mol) dissolved in 500 mL of water is treated over 15 min under stirring with a solution of 0.6 g of $Na_2WO_4 \cdot 2H_2O$ in 112 mL of 30% H_2O_2 at 30–40 °C. The temperature is raised to 80°C and kept at this value for 4 h. The solution is cooled, treated with 0.5 g of 10% Pd/C, heated again, and filtered. The solution is extracted with CH_2Cl_2 (2 × 200 mL, discarted) and taken to dryness. The resulting 3-methyl-2,3-dihydroxybutyric acid is treated with 500 mL of dry methanol saturated with HCl(g). After 16 h at room temperature the mixture is taken to dryness under vacuum, and the residue is dissolved in 500 mL of methanol and evaporated again. The oily ester, without purification, is treated with 100 g (ca. 1 mol) of cyclohexanone and 1 g of 4-toluenesulfonic acid in 500 mL of benzene. The reaction mixture is slowly distilled, until the separation of water in the distillate is ended. The solution is cooled, washed with 50 mL of a saturated solution of $NaHCO_3$, and taken to dryness, and the residue is distilled to give at 90 °C (1 mmHg) 125 g (55% based on the starting acid) of racemic **9d**. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.33. Found: C, 63.20; H, 8.39. A 22-g samples of *rac*-**9d** (0.1 mol) in 70 mL of diethyl ether is added dropwise to 3 g of $LiAlH_4$ in 300 mL of boiling diethyl ether under N_2. After 3 h, ca. 3 mL of ethyl acetate is added dropwise, followed by 50 mL of a saturated solution of sodium potassium tartrate. The organic phase is separated, washed with 50 mL of water, and dried (Na_2SO_4). The residue obtained upon evaporation of the solvent is chromatographed on a column with ca. 150 g of SiO_2 and 15% ethyl acetate in hexane to give *rac*-**10a**, 16.5 g (82%). An analytical sample is prepared by bulb-to-bulb distillation [oven temperature 120 °C (15 mmHg)]. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.05; H, 9.96.

γ-Lactone of (3*R*,4*R*)-3-(Benzoylamino)-4,5-dihydroxy-5-methylhexanoic Acid (13a). A solution of 3 g (0.015 mol) of optically active **10a** in 10 mL of dry CH_2Cl_2 is added at once to 4.84 g of pyridinium chlorochromate in 30 mL of CH_2Cl_2 in the presence of 0.37 g of anhydrous sodium acetate under stirring at room temperature. After 3 h, 50 mL of diethyl ether is added, and the reaction mixture is passed through a short column filled with 30 g of Florisil and 70 g of Na_2SO_4 in diethyl ether. The crude eluate is evaporated to half its volume (ca. 150 mL), treated with 5.5 g of $(C_6H_5)_3P{=}CHCO_2Et$ and 0.1 g of benzoic acid, and refluxed 4 h. The reaction mixture is evaporated to ca. 50 mL and treated with 100 mL of petroleum ether (bp 35–55 °C). The precipitated $(C_6H_5)_3PO$ is filtered and the solution taken to dryness. The oily residue is chromatographed on a column with 200 g of SiO_2, eluting with hexane–ethyl acetate to give 1.4 g of impure **11a** (65% based on recovered **10a** and 1.4 g of unreacted **10a**. An analytical sample of **11a** is obtained by bulb-to-bulb distillation [oven temperature 80–90 °C (ca. 1 mmHg)]. Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.20; H, 9.10.

The ester **11a** (1.4 g, 0.0052 mol) is treated over 5 days at room temperature with 25 mL of dry methanol saturated with NH_3 gas. After that time, the reaction mixture is evaporated, and the residue is dissolved in 100 mL of diethyl ether and extracted twice with 50 mL of 2 N HCl. The acid solution is refluxed 2 h, cooled, extracted with 70 mL of diethyl ether, and then evaporated to dryness under vacuum. The solid residue is dissolved in ca. 50 mL of a saturated solution of $NaHCO_3$ and treated with stirring at room temperature with 0.8 mL of benzoyl chloride in 5 mL of acetone. After 5 h the solution is acidified with acetic acid and soon extracted with ethyl acetate (200 × 2 mL). The oily residue obtained upon evaporation of the dried solution is chromatographed on a column with 100 g of SiO_2 with ethyl acetate–hexane to give as the sole product oily **13a**: 0.68 g (50%); $[\alpha]^{20}_D$ +17.3° (*c* 0.5, MeOH). Anal. Calcd for $C_{14}H_{17}O_4N$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.91; H, 6.61; N, 5.35.

***N*-Benzoyl Derivative of the 5-*C*-Methyl Analogue of L-Acosamine (15a).** To a solution of 0.5 g (0.002 mol) of lactone **13a** in 40 mL of dry tetrahydrofuran is added, with stirring at −40 °C, 6.4 mL of a 1 M solution of diisobutylaluminum hydride in toluene under N_2. After 3 h at the same temperature, 20 mL of a 1:1 mixture of acetone–methanol is added. The precipitate is filtered and washed several times with the above mixture, and the organic phase is taken to dryness. The residue is recrystallized from boiling ethyl acetate–hexane to yield crystalline **15a**: 0.42 g (80%); mp 65 °C; $[\alpha]^{20}_D$ +22.8° (*c* 0.5, MeOH, after 15 min). Anal. Calcd for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.46; H, 7.30; N, 5.23.

Racemic Modification of the *N*-Trifluoroacetyl Lactones 13b and 14. The racemic modification of **11a** (12.8, 0.5 mol; prepared from *rac*-**10a**) is treated with ammonia in methanol as reported above. The residue obtained by taking to dryness the acidic solution is suspended in 100 mL of CH_2Cl_2 and treated

(26) Schaffer, G. W.; Duerr, A. B.; Purzycki, K. L. *J. Org. Chem.* **1972**, *37*, 25.

(27) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

under stirring at −10 °C with 50 mL of $(CF_3CO)_2O$. The reaction mixture is kept at room temperature overnight and taken to dryness under vacuum. The residue is treated twice with ca. 80 mL of a 1:1 mixture of methanol–ethyl acetate. The solid residue, (ca. 5.5 g, 50%), as shown by NMR studies (see text and tables), contains the lactones **13b** and **14** in ca. a 10:1 ratio. Two grams of the latter mixture is chromatographed in a column with 200 g of SiO_2 with hexane–ethyl acetate to yield ca. 150 mg of the δ-lactone **14** (NMR, see text), ca. 150 mg of a mixture of **14** and **13b**, and, eventually, 1.6 g of **13b** (NMR, see text).

***rac*-15b,c.** The lactone **13b** (1.2 g, 0.005 mol) in 50 mL of dry tetrahydrofuran is treated at −40 °C in the presence of N_2 under stirring with 15 mL of a 1 M solution of diisobutylaluminum hydride in toluene. After 4 h the reaction mixture is worked up as above to give eventually a thick oily residue which is chromatographed on a SiO_2 column to give 0.7 g (58%) of oily **15b,c** (NMR, see text).

Isopropylidene Derivative of (5*R*,6*S*)-5,6-Dihydroxy-3-hepten-2-one (18). A solution of 17.8 g (0.1 mol) of (2*S*,3*R*)-5-phenyl-4-pentene-2,3-diol (**2a**)[11] in 200 mL of benzene is treated with 50 mL of 2,2-dimethoxypropane and 0.1 g of 4-toluenesulfonic acid at room temperature for 4 h. The reaction mixture is washed with 50 mL of a saturated solution of $NaHCO_3$ and taken to dryness. The oily residue is chromatographed through a short SiO_2 column with hexane to give 20 g (92%) of oily **8a**, $[\alpha]^{20}_D$ −2.45° (neat). An analytical sample is obtained by bulb-to-bulb distillation [oven temperature 120 °C (2 mmHg)]. Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.95; H, 8.36. A solution of 18 g (0.083 mol) of **8a** in ca. 100 mL dry CH_2Cl_2 is treated with ozonised oxygen at −20 °C until the absorption is complete. Then N_2 is fluxed through, and under stirring at −20 °C 21.7 g of triphenylphosphine (0.083 mol) is added portionwise. After 30 min, a solution of 47.5 g of $(C_6H_5)_3P{=}CHCOCH_3$ in 200 mL of CH_2Cl_2 and 0.1 g of benzoic acid are added. The temperature is raised from −20 °C to reflux and kept there for 2 h. Then, most of the solvent is evaporated, and the residue is treated with ca. 300 mL of diethyl ether–hexane (2:1). The $(C_6H_5)_3PO$ so precipitated is filtered and washed with the above mixture. The solvents are evaporated, and the oily residue is chromatographed on a column with 300 g of SiO_2 with hexane–ethyl acetate to give benzalacetone and compound **18**: oil; $[\alpha]^{20}_D$ +1.7° (*c* 1, EtOH); 11 g (72%); NMR ($CDCl_3$) δ 6.66 (H-4), 6.28 (H-3, $J_{H\text{-}3,H\text{-}4}$ = 15.0 Hz), 4.67 (H-5), 4.41 (H-6, $J_{4,5}$ = 6 Hz, $J_{5,6}$ = 6 Hz, $J_{6,7\text{-}Me}$ = 6 Hz); 2.27 (COMe), 1.50 and 1.38 (2 s, 2 CH_3), 1.15 (7-Me, d). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.30; H, 8.81.

***N*-Benzoyl Derivative of the 1-*C*-Methyl Analogue of L-Acosamine (19a).** The ketone **18** (10 g, 0.054 mol) is treated over 5 days with 100 mL of dry methanol saturated with NH_3 gas at room temperature. The solution is taken to dryness and partitioned between 100 mL of diethyl ether and 70 mL of 2 N HCl. The aqueous phase is refluxed for 2 h and then evaporated to give a solid residue. This separates from boiling ethyl acetate a crystalline solid: mp 98 °C; $[\alpha]^{20}_D$ −65° (*c* 1, EtOH); 5.4 g (55%). The crystalline material (3.6 g in 60 mL of water) is treated dropwise with 3.1 g (0.022 mol) of benzoyl chloride in 50 mL of acetone, adding solid K_2CO_3 to keep the solution at pH 8–9. The reaction mixture is extracted after 3 h with ethyl acetate (200 × 3 mL). The dried (Na_2SO_4) organic phase, upon evaporation, gives 4.2 g (80%) of **19a**: mp 162 °C (from ethyl acetate); $[\alpha]^{20}_D$ −27.5° (*c* 1, EtOH). Anal. Calcd for $C_{14}H_{19}O_4N$: C, 63.38; H, 7.22. Found: C, 63.26; H, 7.18.

***N*-Trifluoroacetyl Derivative of the 1-*C*-Methyl Analogue of L-Acosamine (19b).** The crystalline amino sugar hydrochloride (mp 98 °C; 1 g, 0.0055 mol) suspended in 15 mL of CH_2Cl_2 is treated under stirring at −10 °C with 8 mL of $(CF_3CO)_2O$, keeping the reaction mixture at that temperature overnight. The solvent is evaporated, and the solid residue is chromatographed on a column with 60 g of SiO_2 with hexane–ethyl acetate to give as the sole product **19b**: 1.1 g (83%); mp 144–145 °C (from ethyl acetate-hexane); $[\alpha]^{20}_D$ −27.3° (*c* 1, EtOH); NMR, see text.

***N*-Trifluoroacetyl Derivative of Racemic 5-*C*-Methyl-2,3,4,6-tetradeoxy-3-aminohexose (25).** 2-Methyl-4-penten-2-ol[28] (5.4 g) in 150 mL of CH_2Cl_2 is ozonized at −20 °C until the absorption is ended. Nitrogen is fluxed through for 10 min, and then 14.2 g of $(C_6H_5)_3P$ is added portionwise. After 30 min at the same temperature 37.5 g of $(C_6H_5)_3P{=}CHCO_2Et$ (2 molar equiv) in 100 mL of CH_2Cl_2 and 0.1 g of benzoic acid are added. The reaction mixture is warmed up and refluxed for 2 h. The solvent is evaporated, and the residue is treated with diethyl ether–hexane (1:3, ca. 300 mL), separating by filtration the precipitated $(C_6H_5)_3PO$. The oily residue obtained upon evaporation of the solvent is chromatographed on 150 g of SiO_2 with hexane–ethyl acetate (95:5) to give ca. 7.7 g of **22**. An analytical sample is obtained by bulb-to-bulb distillation [oven temperature 80–100 °C (1 mmHg)]: ^1H NMR ($CDCl_3$) δ 6.95 (dd, H-3), 5.88 (m, H-2), 4.20 (q, CH_2CH_3), 2.36 (dd, H-4), 1.28 (t, CH_2CH_3), 1.25 (s, 6 H, Me_2C). Anal. Calcd for $C_9H_{16}O_3$: C, 62.76; H, 9.36. Found: C, 62.84; H, 9.31. The ester **22** (7.7 g) is treated for 5 days with 60 mL of methanol saturated with dry ammonia at room temperature. The solvent is evaporated, the residue is taken up with 80 mL of 2 N HCl, and the cloudy mixture is extracted with 100 mL of diethyl ether (discarted). The aqueous solution is refluxed 2 h and then taken to dryness. The solid residue is suspended in 50 mL of CH_2Cl_2 and treated under stirring at −10 °C with 30 mL of $(CF_3CO)_2O$. After 16 h at the same temperature, the solvents are evaporated, and the solid residue is crystallized from ethyl acetate–hexane to give ca. 3.3 g (50%) of lactone **24**: mp 105 °C; NMR, see text. Lactone **24** (3.3 g) in 70 mL of dry tetrahydrofuran is treated under stirring at −50 °C with ca. 28 mL of 1 M diisobutylaluminum hydride in toluene (2 molar equiv) under N_2. After 4 h at that temperature, acetone–methanol (1:2, 40 mL) is added. The precipitate is filtered and washed with acetone–methanol, and the organic phase is evaporated. The residue is chromatographed on 150 g of SiO_2 to give with increasing amounts of ethyl acetate in hexane unreacted **24** (ca. 0.8 g) and a crystalline sugar derivative. From ethyl acetate with a small amount of hexane precipitated 1 g (30%) of **25**: mp 151 °C; NMR, see text.

Acknowledgment. We thank Farmitalia-Carlo Erba, Milano, for grants (to G.P.F. and L.M.). This work has been financially supported by Piano Finalizzato CNR Chimica Fine e Secondaria.

Registry No. 1b, 15174-47-7; **2a**, 67470-74-0; **3b**, 55131-20-9; **5a**, 82010-32-0; **5b**, 78687-49-7; **7b**, 82010-33-1; **8a**, 82043-31-0; **8b**, 82010-34-2; **9a**, 82010-35-3; **9b**, 82010-36-4; **9c**, 82010-37-5; **9d**, 82010-38-6; (*R*)-**10a**, 82010-39-7; *rac*-**10a**, 82043-32-1; **10b**, 82010-40-0; **11a**, 82010-41-1; **11b**, 82010-42-2; **12**, 82010-43-3; **13a**, 82010-44-4; **13b**, 82010-45-5; **14**, 82010-46-6; **15a**, 82010-47-7; *rac*-**15b**, 82010-48-8; *rac*-**15c**, 82010-49-9; **16b**, 82010-50-2; **17a**, 82010-51-3; **17b**, 81703-33-5; **18**, 82010-52-4; **19a**, 82010-53-5; **19b**, 82010-54-6; **20**, 81653-06-7; **21**, 39850-35-6; **22**, 82010-55-7; **24**, 82010-56-8; **25**, 82010-57-9; 3-methyl-2-butenoic acid, 541-47-9; 3-methyl-2,3-dihydroxybutyric acid, 1756-18-9; *C*-methyl-L-acosamine hydrochloride, 56501-70-3; 2-methyl-4-penten-2-ol, 624-97-5.

(28) Gottwald Fischer, F. *Chem. Ber.* **1943**, *76*, 735.

(29) Chemical shifts are in parts per million from internal Me_4Si. Melting points were taken on a Kofler hot-stage microscope.