eluted with benzene to yield **11b** (1.51 g, 93%): mp 233–234 °C; NMR (500 MHz) δ 2.33 (s, 3, CH_3), 7.23 (s, 1, H_6), 7.78 (d, 1, H_7, J = 1.1 Hz), 7.9–8.2 (m, 6, Ar), 8.63 (d, 1, H_{11}, J = 7.5 Hz). Anal. Calcd for $C_{20}H_{12}O_2$: C, 84.50; H, 4.25. Found: C, 84.38; H, 4.34.

2-Methyl-3*H*-naphtho[2,1-*b*]pyran-3-one (8b): 39%; mp 159–160 °C; the 500-MHz ^1H NMR spectrum of **8b** was essentially identical with that of an authentic sample of **8b** prepared via the reaction with lithio-*N*,*N*-dimethylpropionamide.

3-Methyl-2*H*-anthra[1,2-*b*]pyran-2-one (9b): 58%; mp 189 °C (sharp); NMR (500 MHz) δ 2.33 (d, 3, CH_3, J = 1.3 Hz), 7.37 (d, 1, H_5, $J_{5,6}$ = 8.7 Hz), 7.56 (m, 2, $H_{5,8}$), 7.66 (d, 1, H_4, J = 1.3 Hz), 7.80 (d, 1, H_6, J = 8.7 Hz), 8.02 (m, 1, $H_{9 \text{ or } 10}$), 8.12 (m, 1, $H_{9 \text{ or } 10}$), 8.41 (s, 1, H_7), 9.14 (s, 1, H_{12}); the assignment of the multiplets at δ 7.56, 8.02, and 8.12 may be reversed. Anal. Calcd for $C_{18}H_{12}O_2$: C, 83.06; H, 4.64. Found: C, 82.95; H, 4.70.

2-Methyl-3*H*-anthra[2,1-*b*]pyran-3-one (10b): 62%; mp 173–175 °C (EtOAc); NMR (500 MHz) δ 2.38 (d, 3, CH_3, J = 1.1 Hz), 7.42 (d, 1, H_3, J = 9.2 Hz), 7.54 (m, 2, $H_{9,10}$), 8.04 (m, 3, $H_{6,8,10}$), 8.45 (s, 1, H_7), 8.46 (br s, 1, H_1), 8.73 (s, 1, H_{12}). Anal. Calcd for $C_{18}C_{12}O_2$: C, 83.06; H, 4.64. Found: C, 82.82; H, 4.60.

9-Methyl-8*H*-pyreno[2,1-*b*]pyran-8-one (12b): 89%; mp 154–156 °C; NMR (500 MHz) δ 2.38 (s, 3, CH_3), 7.34 (s, 1, H_6), 7.9–8.3 (m, 6, Ar), 8.38 (d, 1, H_{11}, J = 9.2 Hz), 8.42 (br s, 1, H_{10}); MS, m/e 284. Anal. Calcd for $C_{20}H_{12}O_2$: C, 84.49; H, 4.26. Found: C, 84.54; H, 4.22.

3,7,12-Trimethyl-2*H*-anthra[1,2-*b*]pyran-2-one (20b): 51%; mp 201–203 °C; NMR (500 MHz) δ 2.16 (s, 3, 7-CH_3), 2.19 (d, 3, 3-CH_3, J = 1.0 Hz), 2.50 (s, 3, 12-CH_3), 7.25–7.50 (m, 7, Ar + vinylic). Anal. Calcd for $C_{20}H_{16}O$: C, 83.31; H, 5.59. Found: C, 83.40; H, 5.68.

Acknowledgment. This research was supported by grants from the Council for Tobacco Research (No. 1608) and the National Cancer Institute, DHHS (CA 14599).

Synthesis of Sugar Amino Acids by Triflate Substitution. 2.[1] Free 3- and 4-Amino Acid Deoxyaldopyranoses

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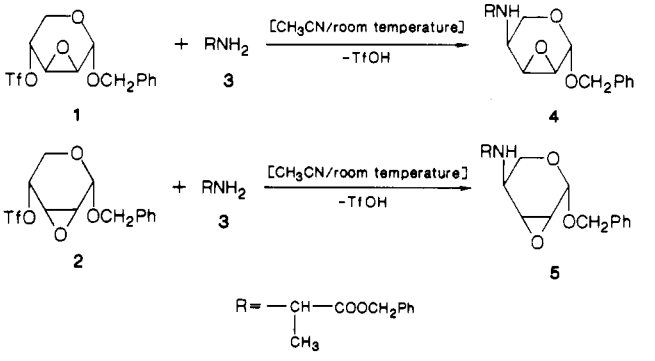
Received November 16, 1987

The S_N2 reactions of benzyl 2,3-anhydro-4-*O*-triflyl-α-D-lyxopyranoside (**1**) and benzyl 2,3-anhydro-4-*O*-triflyl-α-D-ribopyranoside (**2**) with an excess amount of L-alanine benzyl ester in acetonitrile afford benzyl 2,3-anhydro-4-[(L-alanine benzyl ester)-*N*-yl]-4-deoxypyranosides (**4** and **5**, respectively). Acidic hydrolysis of **4** yields **6** and **7** by way of direct epoxide cleavage, while **5** leads via an irreversible isomerization to its corresponding epimine **8**, which further undergoes diaxial ring cleavage, yielding **9** and **10**. Hydrogenation of **10** under neutral or slightly acidic conditions affords the title compound **15**, whereas that of **6** and **9** leads to the 1-L-alanino-1,4-anhydro-1-deoxypentitols **13** and **14**. The 4-L-alanino-4-deoxypentoses **11** and **12** are obtained by hydrogenation of **6** and **9** in a strong acidic medium. High-resolution ^1H and ^{13}C NMR spectroscopy shows that compounds **11** and **12** favor the pyranose at lower and the pyrrolidinose form at higher pH.

Introduction

Although the amine-like coupling of sugars and amino acids vicinal to the anomeric center can be achieved through Amadori or Heyns rearrangement of the corresponding glycosylamines,[2-5] this procedure is not appropriate for the introduction of amino acids at any other site of the carbohydrate moiety. Earlier we reported that the C–N coupling can be done under mild conditions through an S_N2 reaction of amino esters with oxirane-activated sugar triflates (Scheme I).[1,6-8] Stepwise deprotection of the coupling products provides a new class of free 3- and 4-amino-3-deoxy and -4-deoxy aldoses. By contrast, other strategies to synthesize even simple 4-imino-4-deoxy sugars encounter major difficulties.[9,10]

Scheme I



Results and Discussion

Benzyl 2,3-anhydro-4-*O*-triflyl-α-D-lyxopyranoside (**1**) and benzyl 2,3-anhydro-4-*O*-triflyl-α-D-ribopyranoside (**2**)

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(2) Heyns, K.; Breuer, H. *Chem. Ber.* **1958**, *91*, 2750.
(3) Heyns, K.; Breuer, H.; Paulsen, H. *Chem. Ber.* **1957**, *90*, 1374.
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(6) Malik, A.; Kowollik, W.; Scheer, P.; Afza, N.; Voelter, W. *J. Chem. Soc., Chem. Commun.* **1984**, 1229.
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(8) Kowollik, W. Dissertation, Universität Tübingen, 1987.
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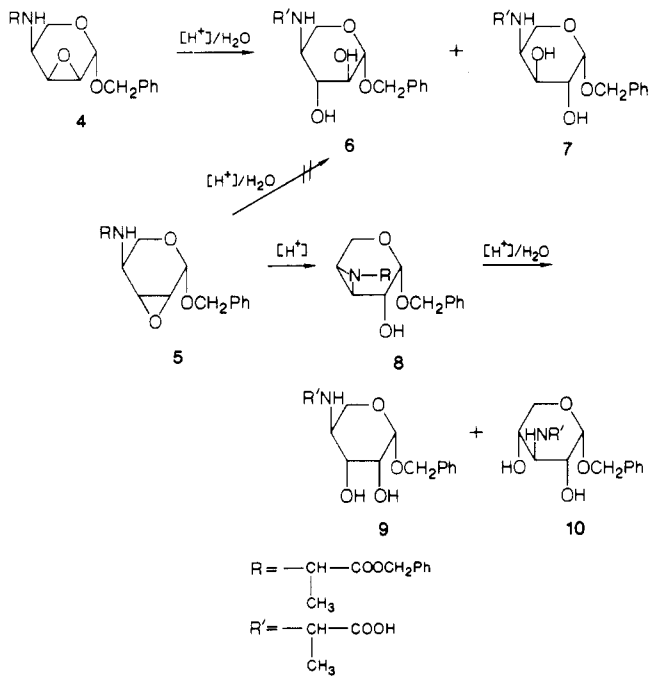
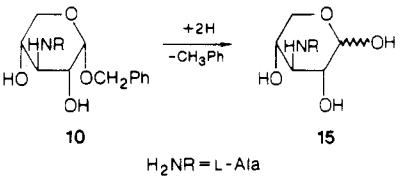
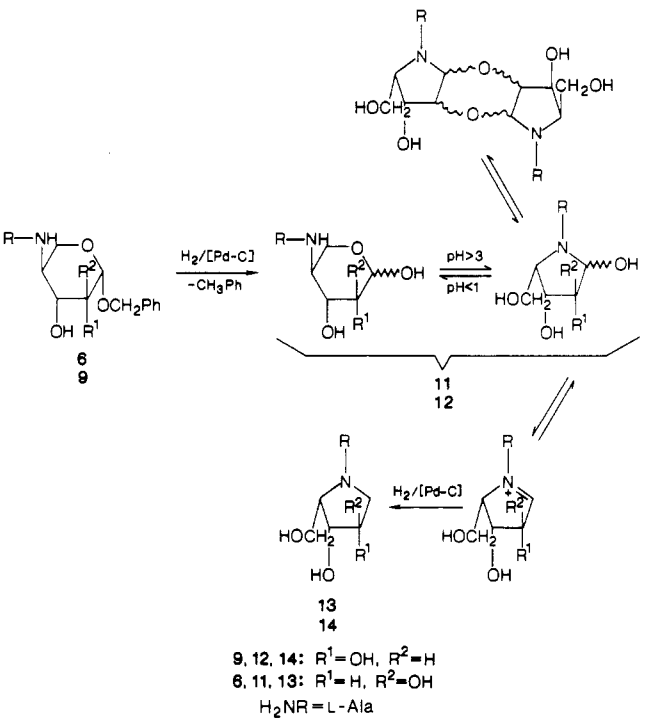
Scheme II



Scheme III



Scheme IV



are the sugar substrates used for this investigation. They are prepared from D-xylose and D-arabinose in four and eight steps, respectively. On the other hand, L-alanine benzyl ester, which serves as the nucleophile, must be used as free base. Attempts to liberate it from its hydrochloride salt in situ during the coupling reaction with sugar triflates **1** and **2** result in the formation of the corresponding 4-chloro-4-deoxy sugars.

The NMR spectral data of benzyl 2,3-anhydro-4-[(L-alanine benzyl ester)-*N*-yl]-4-deoxy-β-L-ribopyranoside (**4**) and benzyl 2,3-anhydro-4-[(L-alanine benzyl ester)-*N*-yl]-4-deoxy-β-L-lyxopyranoside (**5**) indicate the expected preponderance of the $^0H_5$ conformation (**4**: $\delta_{C\text{-}1}$ 94.3 ≃ pseudoaxial anomeric OCH_2 group; $\delta_{1\text{-}H}$ 4.97 ≃ pseudoequatorial anomeric proton; $J_{4,5}$, $J_{4,5}' \leq 4.5$ Hz ≃ pseudoequatorial 4-H. **5**: $\delta_{C\text{-}1}$ 92.3 ≃ pseudoaxial anomeric OCH_2Ph group; $\delta_{1\text{-}H}$ 4.97 ≃ pseudoequatorial anomeric proton; $J_{4,5}$ and $J_{4,5}' \leq 2$ Hz ≃ pseudoequatorial 4-H). Heating of **4** in acetic acid/water (1/1) at 100 °C opens the oxirane ring diaxially in accordance with the Fürst and Plattner rule;[11] simultaneously the ester group is hydrolyzed. Benzyl 4-L-alanino-4-deoxy-β-L-xylopyranoside (**6**) (41%) is obtained as the main product (Scheme II).

The corresponding hydrolysis of **5** proceeds much faster than that of **4**. Instead of the expected products **6** and **7**, which would result from a direct epoxide opening of **5**, benzyl 4-L-alanino-4-deoxy-β-L-lyxopyranoside (**9**) (35%) is isolated as major product and benzyl 3-L-alanino-3-deoxy-α-D-xylopyranoside (**10**) as minor product (6%). The structures of **6**, **9**, and **10** become evident from the ^1H NMR spectroscopic data. In a basic solvent the CH group bearing the imino group is 0.6–0.9 ppm upfield from the other pyranosidic CH groups. This signal is a dd or t in the case of 3-imino-3-deoxy sugars but has a higher multiplicity in the case of 4-imino-4-deoxy sugars. The formation of **9** and **10** can be rationalized through the isomerization of **5** into its intermediate epimine **8**. This is similar to the known oxirane migration[12-14] but is essentially acid catalyzed. Compound **8** is generally formed after treatment of **5** with protic solvents in the presence of weak acids at 20 °C or slightly elevated temperature. However, it is preparatively more efficient to perform the conversion in trimethylsilyl azide/boron trifluoride–etherate (yield 75%). Extended chromatography on silica gel also produces remarkable amounts of **8**. The isomerization is mainly favored by the pseudoaxial position of the imino group in **5**, making nucleophilic attack on the neighboring oxirane carbon atom easier. Compound **4** does not have the required trans relationship between the imino group and oxirane ring, and no isomerization is observed. Compound **8** prefers the $^0H_1$ conformation ($\delta_{C\text{-}1}$ 94.5 ≃ pseudoaxial anomeric OCH_2Ph group; $\delta_{1\text{-}H}$ 4.68 ≃ preponderance of anomeric proton in pseudoequatorial position); here the acidic epimine opening takes place diaxially in accordance with the Fürst and Plattner rule. Catalytic hydrogenation of **10** in water/methanol (Scheme III) yields **15** quantitatively as a colorless solid which is very soluble in water. Compound **15** decomposes into insoluble polymers above 0 °C but is stable at −20 °C. The NMR of **15** shows only the signals of the two pyranose anomers. [Notes to the NMR spectra of the free sugar amino acids: α = α-pyranose, β = β-pyranose, α′ = α-pyrrolidinose, β′ = β-pyrrolidinose. Sometimes doubling of signals is observed, caused by partial racemization of C_α and in the case of **11** and **12** also by an equilibrium between the monomer(s) and the dimer (Scheme IV)]. This indicates that

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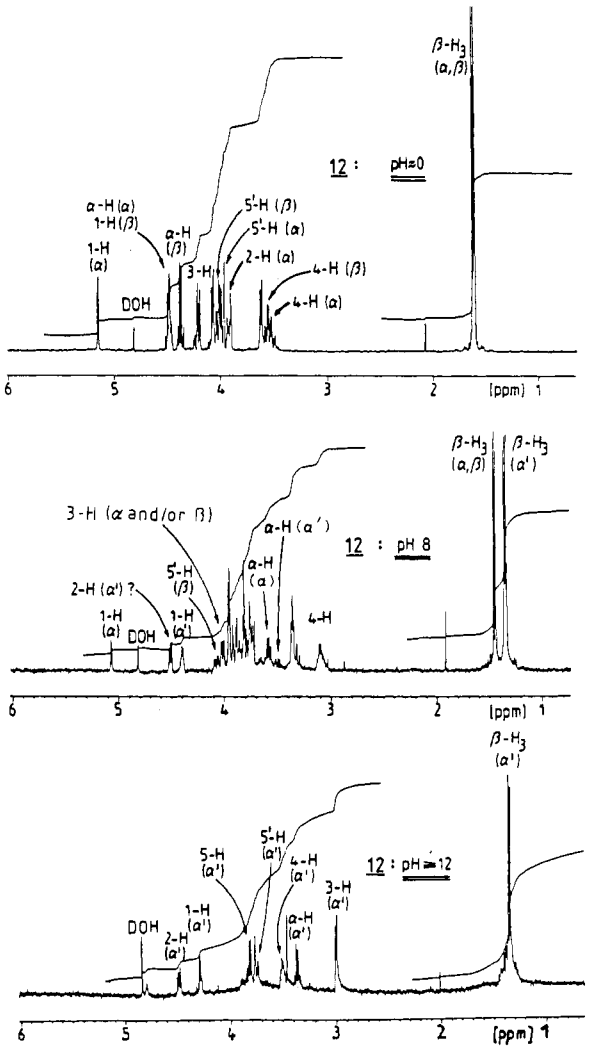

Figure 1. ^{1}H NMR spectra of 4-L-alanino-4-deoxy-L-lyxose (**12**) at different pH values (400 MHz, D_2O, DOH suppressed).

the imino group is not positioned at C-4; the NMR spectra of 4-imino-4-deoxy sugars show a more complex pattern because they comprise also the signals of pyrrolidines and bis(pyrrolidines).

Catalytic hydrogenation of **6** and **9** under the same conditions as described for **10** results in the formation of 1-L-alanino-1,4-anhydro-1-deoxy-L-xylitol (**13**) and 1-L-alanino-1,4-anhydro-1-deoxy-L-lyxitol (**14**) instead of the expected 4-alanino-4-deoxypentoses **11** and **12**, respectively (Scheme IV).[15,16] On hydrogenation of **6** and **9** in acetic acid/water, **11** and **12**, respectively, are observed as intermediates, which further react to yield **13** and **14**, respectively. These final products do not show any color reaction with the orcinol reagent. Only under strong acidic conditions (diluted sulfuric acid) can the nucleophilicity of the nitrogen be sufficiently reduced to supress the formation of the five-membered rings. The free 4-L-alanino-4-deoxypyranoses **11** and **12** are liberated by addition of a sufficient amount of $Ba(OH)_2$ to precipitate all sulfate ions. Careful NMR investigations at different pH values prove that the 4-L-alanino-4-deoxypentoses prefer the pyrrolidine and bis(pyrrolidine) form at basic pH, whereas the pyranose form is strongly favored at acidic pH (Figure 1). The deprotected amino acid deoxy sugars are of limited stability and highly hygroscopic. Studies are under way to investigate the biological properties of the described conjugates of sugars and amino acids, which so far have not been obtained from natural sources.

Experimental Section

Melting points were determined with an apparatus of Büchi company and are not corrected. ^{1}H NMR spectra (TMS as the reference) were obtained from a WM 400 spectrometer and ^{13}C NMR spectra (TMS as the reference) from a WM400 or HFX-90 spectrometer of Bruker Physik AG. An asterisk indicates assignments may be reversed. Elemental analyses were performed with a Perkin-Elmer elemental analyzer, Model 240 B and optical rotations with an OLD Zeiss digital polarimeter. Thin-layer chromatography was carried out with precoated TLC plates (0.25 mm, silica gel 60 F_{254}, Merck) and the solvent systems: A = chloroform/methanol/benzene/water (8/8/8/1); B = toluene/acetone/dichloromethane (1/1/1); C = concentrated NH_3/methanol/chloroform (1/2/2). For quick-column chromatography (QC) 50–55 g of silica gel ("for column chromatography", Merck, i.d. 6.5 cm, $h \approx 5$ cm) and elutions with 20-mL portions of a solvent gradient (increasing polarity, fraction 1 → 80, ethyl acetate/ether/petroleum ether = 1/2/1 → 6/12/4, v/v) were used. The ion-exchange chromatography was performed with a column of 2.8 × 45 cm (Dowex 1 × 8, mesh size 200–400, OH^- form) and ammonium acetate buffer solution with increasing concentration and/or decreasing pH) as eluting solvent.

L-Alanine Benzyl Ester (3). L-Alanine benzyl ester hydrochloride,[17] (28.7 g, 0.13 mol) obtained from L-alanine, benzyl alcohol, and thionyl chloride following a procedure for the synthesis of L-proline benzyl ester hydrochloride,[18] was dissolved in 10 mL of H_2O. Ether (300 mL) and concentrated ammonia solution were added to the mixture, until phenolphthalein changed to red. The ethereal layer was separated and the aqueous phase twice extracted with 50–100 mL of ether. The unified ethereal solutions were dried over sodium sulfate. After filtration and removal of the solvent in vacuo, **3** was obtained as a viscous oil. Yield: 10.1 g (80%). $[\alpha]^{25}_D$ +8° (*c* 1, $CHCl_3$); R_f(A) 0.29. ^{1}H NMR (90 MHz, $CDCl_3$): δ 7.33 (m, 5 H, phenyl), 5.13 (s, 2 H, $COCH_2$), 3.57 (q, 1 H, $J_{\alpha,\beta}$ = 7 Hz, α-H), 1.63 (br s, 2 H, NH_2), 1.33 (d, 3 H, $J_{\beta,\alpha}$ = 2 Hz, β-H_3). $C_{10}H_{13}NO_2$ (179.2). Anal. Calcd: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.10; H, 7.27; N, 7.69.

General Procedure for the Triflate Substitution. A mixture of 4.5 g (25 mmol) of **3**, 25 mL of anhydrous acetonitrile, and 3.54 g (10 mmol) of triflate **1** or **2**[15] was stirred for 12 h at room temperature. After removal of the solvent in vacuo, the residue was dissolved in 150 mL of ethyl acetate, washed with half-saturated Na_2CO_3 solution and water, and dried over sodium sulfate. The product (**4** or **5**) was isolated by filtration, the solvent removed in vacuo, and the residue subjected to QC.

Benzyl 2,3-Anhydro-4-[(L-alanine benzyl ester)-*N*-yl]-4-deoxy-β-L-ribopyranoside (4). Yield: 3.45 g (90%). Mp 43–44 °C (ether/*n*-hexane); $[\alpha]^{25}_D$ +0.7° (*c* 1, $CHCl_3$), R_f(B) 0.59. ^{1}H NMR (400 MHz, $CHCl_3$): δ 7.34 (m, 10, phenyl), 5.18/5.14 (2 d, 2 H, J_{gem} = 12.25 Hz, $COOCH_2$), 4.97 (s, 1 H, 1-H), 4.77/4.53 (2 d, 2 H, J_{gem} = 11.6 Hz, 1-OCH_2), 3.77 (dd, 1 H, $J_{5,5'}$ = 12.1 Hz, $J_{5,4}$ = 4.1 Hz, 5-H), 3.68 (q, 1 H, $J_{\alpha,\beta}$ = 6.9 Hz, α-H), 3.40 (dd, 1 H, $J_{3,4}$ = 4.6 Hz, $J_{3,2}$ = 3.8 Hz, 3-H), 3.29 (ddd, 1 H, $J_{5',5}$ = 12.1 Hz, $J_{5',4}$ = 2.5 Hz, J = 0.85 Hz, 5'-H), 3.15 (d, 1 H, $J_{2,3}$ = 3.8 Hz, 2-H), 3.03 (dt, 1 H, $J_{4,3}$ = $J_{4,5}$ = 4.5 Hz, $J_{4,5'}$ = 2.5 Hz, 4-H), 1.91 (br s, 1 H, NH), 1.37 (d, 3 H, $J_{\beta,\alpha}$ = 6.9 Hz, β-H_3). ^{13}C NMR (22.6 MHz, $CDCl_3$, GASPE): δ 174.9 (α-C=O), 94.3 (C-1), 70.0 (1-OCH_2Ph), 66.5 ($COOCH_2$Ph), 60.1 (C-5), 53.9 (C-α), 51.6 (C-3),* 51.4 (C-2),* 48.0 (C-4), 19.3 (C-β). $C_{22}H_{25}NO_5$ (383.4). Anal. Calcd: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.86; H, 6.57; N, 3.64.

Benzyl 2,3-Anhydro-4-[(L-alanine benzyl ester)-*N*-yl]-4-deoxy-β-L-lyxopyranoside (5). Yield: 3.34 g (87%), oil. $[\alpha]^{25}_D$ +62.1° (*c* 1, $CDCl_3$); R_f(B) 0.61. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (m, 10 H, phenyl), 5.17/5.13 (2 d, 2 H, J_{gem} = 12.2 Hz, $COOCH_2$), 4.97 (d, 1 H, $J_{1,2}$ = 2.5 Hz, 1-H), 4.77/4.58 (2 d, 2 H, J_{gem} = 12.25 Hz, 1-OCH_2), 3.86 (dd, 1 H, $J_{5,5'}$ = 12.05 Hz, $J_{5,4}$ = 2 Hz, 5-H), 3.54 (q, 1 H, $J_{\alpha,\beta}$ = 6.95 Hz, α-H), 3.30 (d, 1 H, $J_{5',5}$

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= 12.05 Hz, 5'-H), 3.23 (m, 2 H, 3-H, 2-H), 2.94 (d, 1 H, $J_{4,5}$ = 2 Hz, 4-H), 1.92 (br s, 1 H, NH), 1.33 (d, 3 H, $J_{\beta,\alpha}$ = 6.85 Hz, β-H_3). ^{13}C NMR (22.6 MHz, $CDCl_3$; GASPE): δ 175.3 (α-C=O), 92.3 (C-1), 69.1 (1-OCH_2Ph) 66.7 ($COOCH_2$Ph), 59.5 (C-5), 55.2 (C-α), 52.0 (C-3),* 51.1 (C-2),* 50.3 (C-4), 19.2 (C-β). $C_{22}H_{25}NO_5$ (383.4). Anal. Calcd: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.59; H, 6.53; N, 3.61.

Partial Acidic Hydrolysis of 4 or 5 (General Procedure). **4** or **5** (3.83 g, 10 mmol) was stirred in 100 mL of acetic acid/water (1/1) at 100 °C until no more starting material could be detected on TLC. After removal of the solvent, water was repeatedly added to the residue followed by evaporation to dryness at 60–80 °C in vacuo. Finally the residue is dissolved in aqueous ammonia, charcoaled, filtered through Celite, and chromatographed on a column of ion-exchange resin.

Benzyl 4-L-Alanino-4-deoxy-β-L-xylopyranoside (6). The residue obtained after Celite filtration of the partial hydrolysis product of **4** (reaction time: 13 h) was dissolved in a small amount of aqueous ammonia and quickly adjusted to pH 7.0–7.3 by addition of acetic acid/water (1/3, v/v). **6** crystallized slowly. Noncrystallyzing mother liquors were put together and freed to a large extent of ammonium acetate by repeated dissolving in water and evaporation to dryness at 60–80 °C. The residue was dissolved in a small amount of aqueous ammonia and chromatographed on DOWEX 1 × 8. Eluent: 700 mL of H_2O → 700 mL of 0.5 N $NH_4^+AcO^-$ → 700 mL of 1.0 N $NH_4^+AcO^-$ → 700 mL of 2 N $NH_4^+AcO^-$.

The fractions were collected in 6-mL portions. After exceeding 0.5 N concentration of the buffer, first traces of low polar impurities were eluted; then **6** appeared, followed by a mixture of **6** and **7**. The unified fractions containing pure **6** were freed of ammonium acetate and crystallized from hot water. Total yield of **6**: 1.28 g (41%). Mp 203–205 °C dec (H_2O); $[\alpha]^{25}_D$ +164° (*c* 1, concentrated ammonia/water (1/3)), R_f(C) 0.51. ^1H NMR (400 MHz, ND_4OD/D_2O): δ 7.33–7.24 (m, 5 H, phenyl), 4.71/4.58 (2 d, 2 H, J_{gem} = 11.6 Hz, 1-OCH_2), 4.33 (d, 1 H, $J_{1,2}$ = 7.7 Hz, 1-H), 3.88 (dd, 1 H, $J_{5',5}$ = 11.85 Hz, $J_{5',4}$ = 5.0 Hz, 5'-H), 3.25 (t, 1 H, $J_{3,2}$ = 9.4 Hz, $J_{3,4}$ = 9.25 Hz, 3-H), 3.23 (q, 1 H, $J_{\alpha,\beta}$ = 6.9 Hz, α-H), 3.16 (t, 1 H, $J_{2,3}$ = 9.4 Hz, $J_{2,1}$ = 7.7 Hz, 2-H), 3.14 (dd, 1 H, $J_{5,5'}$ = 11.85 Hz, $J_{5,4}$ = 10.7 Hz, 5-H), 2.59 (dt, 1 H, $J_{4,3}$ = $J_{4,5}$ = 10.0 Hz, $J_{4,5'}$ = 5.0 Hz, 4-H), 1.11 (d, 3 H, $J_{\beta,\alpha}$ = 6.9 Hz, β-H_3). ^{13}C NMR (100.6 MHz, ND_4OD/D_2O, GASPE): δ 182.9 (α-C=O), 101.9 (C-1), 74.8 (C-3), 73.3 (C-2), 71.3 (1-OCH_2Ph), 64.4 (C-5), 56.7 (C-α), 56.4 (C-4), 18.3 (C-β). $C_{15}H_{21}NO_6$ (311.3). Anal. Calcd: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.30; H, 6.81; N, 4.49.

Benzyl 3,4-Dideoxy-3,4-[epi(alanine benzyl ester)-*N*,*N*-diyl]-β-L-arabinopyranoside (8): **5** (1.0 g, 2.6 mmol) was dissolved in 5 mL of dry ether, 1 mL of trimethylsilyl azide and 0.8 mL of BF_3–etherate. The reaction mixture was stirred at room temperature until the complete conversion of **5** into **8**. After the addition of 10 mL of a 10% $NaHCO_3$ solution, the mixture was further stirred for 15 min and extracted with 100 mL of ethyl acetate, the organic layer washed with a $NaHCO_3$ solution and water, dried over sodium sulfate, and filtered, and the solvent evaporated in vacuo. The residue crystallyzes from ethanol: colorless needles; yield, 0.75 g (75%); mp 101.5 °C (ethyl acetate/*n*-hexane); $[\alpha]^{25}_D$ +73.1° (*c* 1, $CHCl_3$); R_f(B) 0.52. ^1H NMR (400 MHz, $CDCl_3$): δ 7.33 (m, 10 H, phenyl), 5.18/5.11 (2 d, 2 H, J_{gem} = 12.18 Hz, $COOCH_2$), 4.68 (d, 1 H, $J_{1,2}$ = 4.0 Hz, 1-H), 4.77/4.49 (2 d, 2 H, J_{gem} = 11.625 Hz, 1-OCH_2), 3.94 (dd, 1 H, $J_{5',5}$ = 12.1 Hz, $J_{5',4}$ = 3.1 Hz, 5'-H), 3.84 (dd, 1 H, $J_{2,OH}$ = 8.8 Hz, $J_{2,1}$ = 4.0 Hz, 2-H), 3.82 (d, 1 H, $J_{5,5'}$ = 12.1 Hz, 5-H), 2.52 (d, 1 H, $J_{OH,2}$ = 8.8 Hz, OH), 2.34 (q, 1 H, $J_{\alpha,\beta}$ = 6.8 Hz, α-H), 1.93 (dd, 1 H, $J_{4,3}$ = 6.6 Hz, $J_{4,5'}$ = 3.1 Hz, 4-H), 1.86 (d, 1 H, $J_{3,4}$ = 6.6 Hz, 3-H), 1.44 (d, 3 H, $J_{\beta,\alpha}$ = 6.8 Hz, β-H_3). ^{13}C NMR (22.6 MHz, $CDCl_3$, GASPE): δ 171.9 (α-C=O), 94.3 (C-1), 69.9 (1-OCH_2Ph), 66.5 ($COOCH_2$Ph), 65.9 (C-α), 64.8 (C-2), 59.7 (C-5), 40.1 (C-3), 37.2 (C-4), 17.0 (C-β). $C_{22}H_{26}NO_5$ (383.4). Anal. Calcd: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.75; H, 6.56; N, 3.62.

Benzyl 4-L-Alanino-4-deoxy-β-L-lyxopyranoside (9) and Benzyl 3-L-Alanino-3-deoxy-α-D-xylopyranoside (10). The residue obtained after partial acidic hydrolysis of **5** (via intermediate **8**, reaction time, 2.5 h) and subsequent Celite filtration was chromatographed on DOWEX 1 × 8 (see **6**). Eluent: 700 mL of dilute NH_3 (pH ≥10) → 700 mL of 0.5 N $NH_4^+AcO^-$ (pH 8.5) → 700 mL of 1.0 N $NH_4^+AcO^-$ (pH 8.5) → 700 mL 2 N $NH_4^+AcO^-$ (pH 7.0). **9** was eluted first. Yield: 1.09 g (35%). Mp 231 °C (water; dec above 205 °C); $[\alpha]^{23}_D$ +244 (*c* 1, concentrated NH_3/H_2O (1/3)); R_f(C) 0.50. ^1H NMR (400 MHz, ND_4OD/D_2O): δ 7.33–7.28 (m, 5 H, phenyl), 4.72/4.55 (2 d, 2 H, J_{gem} = 12.0 Hz, 1-OCH_2), 4.53 (s, 1 H, 1-H), 3.91 (dd, 1 H, $J_{5',5}$ = 11.9 Hz, $J_{5',4}$ = 4.56 Hz, 5'-H), 3.78 (m, 1 H, 2-H), 3.46 (dd, 1 H, $J_{3,4}$ = 8.8 Hz, $J_{3,2}$ = 3.25 Hz, 3-H), 3.22 (q, 1 H, $J_{\alpha,\beta}$ = 6.9 Hz, α-H), 3.09 (dd, 1 H, $J_{5,5'}$ = 11.9 Hz, $J_{5,4}$ = 9.0 Hz, 5-H), 2.77 (dt, 1 H, $J_{4,3}$ = $J_{4,5}$ = 8.8 Hz, $J_{4,5'}$ = 4.54 Hz, 4-H), 1.11 (d, 3 H, $J_{\beta,\alpha}$ = 6.9 Hz, β-H_3). ^{13}C NMR (100.6 MHz, ND_4OD/D_2O (GASPE): δ 182.9 (α-C=O), 99.1 (C-1), 71.4 (C-3), 70.5 (1-OCH_2Ph), 68.7 (C-2), 63.1 (C-5), 56.7 (C-α), 53.1 (C-4), 18.3 (C-β). $C_{15}H_{21}NO_6$ (311.3). Anal. Calcd: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.69; H, 6.81; N, 4.45.

After elution of **9**, a mixture of **9**, **10**, and a low polar component (R_f(C) 0.83) were eluted. Finally pure **10** appears, whose elution is completed by 2 N acetic acid. Yield: 0.18 g (6%). Long colorless needles; mp 230–233 °C (water; dec above 215 °C); $[\alpha]^{23}_D$ +250 ° (*c* 1, concentrated NH_3/H_2O (1/3)); R_f(C) 0.54. ^1H NMR (400 MHz, ND_4OD/D_2O): δ 7.34–7.24 (m, phenyl), 4.75 (d, 1 H, $J_{1,2}$ = 3.7 Hz, 1-H), 4.61/4.45 (2 d, 2 H, J_{gem} = 11.84 Hz, 1-OCH_2), 3.52 (ddd, 1 H, $J_{4,5'}$ = 11.2 Hz, $J_{4,3}$ = 9.2 Hz, $J_{4,5}$ = 7.2 Hz, 4-H), 3.42 (q, 1 H, $J_{\alpha,\beta}$ = 7 Hz, α-H), 3.43–3.38 (m, 2 H, 5-H, 5'-H), 3.38 (dd, 1 H, $J_{2,3}$ = 10.1 Hz, $J_{2,1}$ = 3.7 Hz, 2-H), 2.59 (t, 1 H, $J_{3,2}$ = $J_{3,4}$ = 9.6 Hz, 3-H), 1.11 (d, 3 H, $J_{\beta,\alpha}$ = 7 Hz, β-H_3). ^{13}C NMR (100.6 MHz, ND_4OD/D_2O, GASPE): δ 183.7 (α-C=O), 97.0 (C-1), 71.5 (C-2), 69.3 (1-OCH_2Ph), 68.3 (C-4), 61.6 (C-5), 60.0 (C-3), 57.9 (C-α), 19.0 (C-β). $C_{15}H_{21}NO_6$ (311.3). Anal. Calcd: C, 57.87; H, 6.80; N, 4.50. Found: C, 57.81; H, 6.78; N, 4.49.

L-Alanino-4-deoxy-L-xylose (11). **6** (200 mg, 0.64 mmol) was hydrogenated in 2.0 mL of 2 N H_2SO_4 in the presence of 200 mg of hydrogenation catalyst (10% Pd on charcoal; Merck) at 0 °C/1 atm H_2 till complete conversion of **6** into **11** (3.5 h). A sufficient amount of saturated barium hydroxide solution was added to bind all sulfuric acid. The mixture was charcoaled and filtered through Celite. After freeze-drying of the filtrate, the residue was immediately stored at −20 °C. The yield was almost quantitative: white fluffy powder, dec above 90 °C. $[\alpha]^{23}_D$ +1.5° (*c* 4.7, 1.3 N H_2SO_4); R_f(C) 0.49. ^1H NMR (400 MHz, D_2O pH ≈0): δ 5.23 (d, $J_{1,2}$ = 3.4 Hz, 1-H(α)), 4.63 (d, $J_{1,2}$ = 7.8 Hz, 1-H(β)), 4.37 (q, $J_{\alpha,\beta}$ = 7.2 Hz, α-H), 4.26 (dd, $J_{5',5}$ = 11.8 Hz, $J_{5',4}$ = 4.9 Hz, 5'-H(β)), 4.11 (m, 5-H(α)), 4.07 (dd, $J_{3,4}$ = 10.1 Hz, $J_{3,2}$ = 8.8 Hz, 3-H(β)), 4.02 (m, 5'-H(α)), 3.83 (dd, $J_{3,4}$ = 9.2 Hz, $J_{3,2}$ = 8.6 Hz, 3-H(α)), 3.65 (m, 5-H(β)), 3.62 (dd, $J_{2,3}$ = 8.6 Hz, $J_{2,1}$ = 3.4 Hz, 2-H(α)), 3.45 (dt, $J_{4,3}$ = 10.1 Hz, $J_{4,5}$ = 10 Hz, $J_{4,5'}$ = 4.9 Hz, 4-H(β)), 3.43 (ddd, $J_{4,5}$ = 10.2 Hz, $J_{4,3}$ = 9.2 Hz, $J_{4,5'}$ = 5.0 Hz, 4-H(α)), 3.32 (dd, $J_{2,3}$ = 8.8 Hz, $J_{2,1}$ = 7.8 Hz, 2-H(β)), 1.64 (d, $J_{\beta,\alpha}$ = 7.2 Hz, β-H_3(α)), 1.63 (d, $J_{\beta,\alpha}$ = 7.2 Hz, β-H_3(β)). ^1H NMR (400 MHz, D_2O, pH ≥12): δ 5.30 (d, $J_{1,2}$ = 3.3 Hz, 1-H(α)), 4.67 (m, 1-H(β)), 4.33 (m, 5'-H(β)), 4.16 (t, $J_{2,1}$ = $J_{2,3}$ = 4.5 Hz, 2-H(β')), 3.78 (dd, $J_{5,5'}$ = 12.0 Hz, $J_{5,4}$ = 6.1 Hz, 5-H(α',β')), 3.72 (dd, $J_{5',5}$ = 12.0 Hz, $J_{5',4}$ = 3.6 Hz, 5'-H(α',β')), 3.47 (q, $J_{\alpha,\beta}$ = 6.9 Hz, α-H(α',β')), 3.25 (m, 2-H(β)), 2.82 (m, 4-H(α,β)), 1.4 (d, $J_{\beta,\alpha}$ = 6.7 Hz, β-H_3(α,β)), 1.35 (d, $J_{\beta,\alpha}$ = 6.9 Hz, β-H_3(α',β'). ^{13}C NMR (100.6 MHz, D_2O, pH ≈0, GASPE): δ 174.2 (α-C=O(α)), 174.1 (α-C=O(β)), 173.8 (α-C=O(β')), 98.9 (C-1(β)), 94.6 (C-1(α)), 77.4 (C-1(β')), 76.7 (C-3(β)), 75.3 (C-3(β')), 74.2 (C-2(β,β')), 73.8 (C-3(α)), 70.9 (C-2(α)), 70.2 (C-4(β)), 63.1 (C-5(β)), C-α(β')), 59.5 (C-5(α)), 58.8 (C-4(α)), 58.7 (C-5(β')), 58.6 (C-4(β)), 57.8 (C-α(β)), 57.6 (C-α(α)), 16.9 (C-β(β)), 16.8 (C-β(α)), 13.5 (C-β(β')). $C_8H_{15}NO_6$ (221.2). Anal. Calcd: C, 43.44; H, 6.84; N, 6.33. Found: C, 36.43; H, 5.98; N, 5.29.

4-L-Alanino-4-deoxy-L-lyxose (12). **12** was synthesized from **9** by using the procedure described above for **11**. Brownish amorphous compound, mp >200 °C (dec above 110 °C); $[\alpha]^{23}_D$ +62° (*c* 4.7, 1.3 N H_2SO_4); R_f(C) = 0.69. ^1H NMR (400 MHz, D_2O, pH ≈0): δ 5.14 (d, $J_{1,2}$ = 2.7 Hz, 1-H(α)), 4.48 (q, $J_{\alpha,\beta}$ = 7.2 Hz, α-H(α)), 4.47 (d, $J_{1,2}$ = 4.2 Hz, 1-H(β)), 4.37 (q, $J_{\alpha,\beta}$ = 7.2 Hz, α-H(β)), 4.22 (dd, $J_{3,4}$ = 10.5 Hz, $J_{3,2}$ = 3.4 Hz, 3-H(α)), 4.20 (dd, $J_{3,4}$ = 9.8 Hz, $J_{3,2}$ = 3.4 Hz, 3-H(β)), 4.01 (dd, $J_{5',5}$ = 13.6 Hz, $J_{5',4}$ = 5.4 Hz, 5'-H(β)), 3.94 (dd, $J_{5',5}$ = 13.5 Hz, $J_{5',4}$ = 5.0 Hz, 5'-H(α)), 3.89 (dd, $J_{2,3}$ = 3.4 Hz, $J_{2,1}$ = 2.7 Hz, 2-H(α)), 3.54 (ddd, $J_{4,5}$ = 10.2 Hz, $J_{4,3}$ = 9.8 Hz, $J_{4,5'}$ = 5.4 Hz, 4-H(β)), 3.48 (dt, $J_{3,4}$ = $J_{4,5}$ = 10.5 Hz, $J_{4,5'}$ = 5.0 Hz, 4-H(α)), 1.62 (d, $J_{\beta,\alpha}$ = 7.2 Hz, β-H_3(α)), 1.61 (d, $J_{\beta,\alpha}$ = 7.2 Hz, β-H_3(β)). ^1H NMR (400 MHz, D_2O, pH 8): δ 5.06 (d, $J_{1,2}$ = 3.7 Hz, 1-H(α)), 4.50 (dd, $J_{2,3}$ = 6.5 Hz, $J_{2,1}$ = 4.5 Hz, 2-H(α')), 4.39 (d, $J_{1,2}$ = 4.5 Hz, 1-H(α')), 4.06 (m, 5'-H(β)),

4.01 (dd, $J_{3,4}$ = 8.4 Hz, $J_{3,2}$ = 3.2 Hz, 3-H(α,β)), 3.58 (q, $J_{\alpha,\beta}$ = 7.0 Hz, α-H(α')), 3.50 (q, $J_{\alpha,\beta}$ = 7.15 Hz, α-H(α)), 3.10 (dt, $J_{4,3}$ = $J_{4,5}$ = 8.1 Hz, $J_{4,5'}$ = 4.1 Hz, 4-H(α')), 1.45 (d, $J_{\beta,\alpha}$ = 7.15 Hz, β-H$_3$(α,β)), 1.35 (d, $J_{\beta,\alpha}$ = 7.0 Hz, β-H$_3$(α'). ^{1}H NMR (400 MHz, D_2O, pH $\geq$12): δ 4.48 (dd, $J_{2,3}$ = 8.1 Hz, $J_{2,1}$ = 4.8 Hz, 2-H(α')), 4.28 (d, $J_{1,2}$ = 4.8 Hz, 1-H(α')), 3.82 (dd, $J_{5,5'}$ = 11.5 Hz, $J_{5,4}$ = 6.1 Hz, 5-H(α')), 3.75 (dd, $J_{5',5}$ = 11.5 Hz, $J_{5',4}$ = 3.8 Hz, 5'-H(α')), 3.49 (ddd, $J_{4,3}$ = 8.4 Hz, $J_{4,5}$ = 6.1 Hz, $J_{4,5'}$ = 3.8 Hz, 4-H(α')), 3.36 (q, $J_{\alpha,\beta}$ = 7.1 Hz, α-H(α')), 3.00 (dd, $J_{3,4}$ = 8.4 Hz, $J_{3,2}$ = 8.1 Hz, 3-H(α')), 1.35 (d, $J_{\beta,\alpha}$ = 7.1 Hz, β-H$_3$(α')). ^{13}C NMR (100.6 MHz, D_2O, pH $\approx$0, GASPE): δ 174.2 (α-C=O(α,β)), 173.5 (α-C=O(α')), 96.7 (C-1(β)), 96.5 (C-1(α)), 72.7/72.2 (C-3(α)), 72.7 (C-1(α'), C-3(α')), 71.8/71.5 (C-3(β)), 71.5 (C-2(α')), 70.1 (C-2(β)), 69.0 (C-2(α), C-4(α')), 63.4 (C-α(α')), 63.1 (C-5(β)), 59.8/59.7 (C-5(α)), 58.0 (C-4(α)), 57.9 (C-4(β)), 56.8 (C-α(α)), 56.3 (C-α(β)), 55.9 (C-5(α')), 16.9 (C-β(α,β)), 13.2 (C-β(α')). ^{13}C NMR (100.6 MHz, D_2O, pH $\approx$8, GASPE): δ 178.3 (α-C=O(α')), 96.7 (C-1(α)), 73.2 (C-3(α')), 72.3 (C-1(α')), 72.1 (CH_2), 71.9 (C-2(α')), 68.3 (C-4(α')), 65.4 (C-α(α')), 64.3 (CH), 61.3 (C-5(β)), 59.9 (C-5(α)), 55.8 (C-5(α')), 19.9 (C-β(β)), 18.8 (C-β(α)), 14.8 (C-β(α')). $C_8H_{15}NO_6$ (221.2). Anal. Calcd: C, 43.44; H, 6.84; N, 6.33. Found: C, 32.52; H, 5.06; N, 4.79.

1-L-Alanino-1,4-anhydro-1-deoxy-L-lyxitol (14). **9** (200 mg, 0.64 mmol) was completely dissolved in 10–15 mL of H_2O and hydrogenated to completion in the presence of 200 mg catalyst (10% Pd on charcoal, Merck) at 1 atm H_2 (about 2 h). Charcoal was added, and the mixture was filtered through Celite. After freeze-drying, **14** was obtained as a brown syrupy mass. $[\alpha]^{21}_D$ +46.0° (*c* 1, H_2O); $[\alpha]^{21}_D$ +47.7° (*c* 0.5, H_2O); R_f(C) 0.56. ^{13}C NMR (100.6 MHz, D_2O, GASPE): δ 174.0 (α-C=O), 73.0 (C-3), 71.7 (C-2), 68.9 (C-4), 65.6 (C-α), 59.3 (C-1), 55.6 (C-5), 14.2 (C-β). $C_8H_{15}NO_5$ (205.2). Anal. Calcd: C, 46.82; H, 7.37; N, 6.83. Found: C, 41.62; H, 7.74; N, 6.65.

3-L-Alanino-3-desoxy-D-xylose (15). **10** (200 mg, 0.64 mmol) was dissolved in methanol/water (1/2) and hydrogenated as described above for **14** (about 2.5 h). After repeated freeze-drying, **15** was obtained as a white, fluffy powder, dec above 120–125 °C; $[\alpha]^{23}_D$ +49.3° (*c* 2, H_2O); R_f(C) 0.50. ^{1}H NMR (400 MHz, D_2O): δ 5.22/5.21 (d, $J_{1,2}$ = 3.6 Hz, 1-H(α)), 4.66/4.64 (d, $J_{1,2}$ = 7.6 Hz, 1-H(β)), 4.23 (q, $J_{\alpha,\beta}$ = 7.2 Hz, α-H(α)), 4.19 (q, $J_{\alpha,\beta}$ = 7.2 Hz, α-H(β)), 4.02/4.00 (dd, $J_{5,5'}$ = 11.3 Hz, $J_{5,4}$ = 5 Hz, 5-H(β)), 4.00 (ddd, $J_{4,5'}$ = 10.5 Hz, $J_{4,3}$ = 9.55 Hz, $J_{4,5}$ = 5 Hz, 4-H(α,β)), 3.96 (dd, $J_{5',5}$ = 11.3 Hz, $J_{5',4}$ = 10.5 Hz, 5'-H(α)), 3.84/3.75 (dd, $J_{2,3}$ = 10.65 Hz, $J_{2,1}$ = 3.6 Hz, 2-H(α)), 3.75 (dd, $J_{5,5'}$ = 11.3 Hz, $J_{5,4}$ = 5 Hz, 5-H(α)), 3.56/3.50 (dd, $J_{2,3}$ = 10.4 Hz, $J_{2,1}$ = 7.6 Hz, 2-H(β)), 3.43 (dd, $J_{5',5}$ = 11.3 Hz, $J_{5',4}$ = 10.5 Hz, 5'-H(β)), 3.41 (dd, $J_{3,2}$ = 10.4 Hz, $J_{3,4}$ = 10.2 Hz, 3-H(β)), 3.30/3.29 (dd, $J_{3,2}$ = 10.65 Hz, $J_{3,4}$ = 9.55 Hz, 3-H(α)), 1.57 (d, $J_{\beta,\alpha}$ = 7.2 Hz, β-H$_3$(α,β)). ^{13}C NMR (100.6 MHz, D_2O, GASPE): δ 177.3 (α-C=O(α,β)), 99.2/99.1 (C-1(β)), 93.8/93.7 (C-1(α)), 72.6 (C-2(β)), 70.4 (C-2(α)), 68.6/68.5 (C-5(β)), 68.2 (C-4(β)), 68.7 (C-4(α)), 65.8 (C-3(β)), 63.4/63.0 (C-3(α)), 63.3 (C-5(α)), 60.5/60.4 (C-α(β)), 60.2 (C-α(α)), 18.4/17.8 (C-β(α)), 18.2 (C-β(β)). $C_8H_{15}NO_6$ (221.2). Anal. Calcd: C, 43.44; H, 6.84; N, 6.33. Found: C, 38.22; H, 6.50; N, 5.93.

New Stereoselective Synthesis of 20*S* and 20*R* Steroidal Side Chains. Remarkable Stereoselectivity Differences between Saturated and α,β-Unsaturated Steroidal Esters

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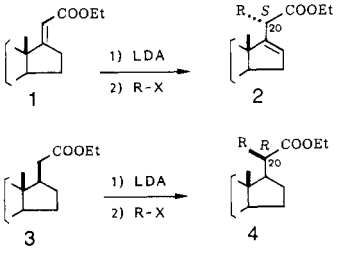
Received April 19, 1988

Reaction of (*E*)-ethyl 3β-(*tert*-butyldimethylsiloxy)pregna-5,17(20)-dien-21-oate (**5**), (*E*)-ethyl 3β-(*tert*-butyldimethylsiloxy)-5α-pregn-17(20)-en-21-oate (**13**), and (*E*)-ethyl 6β-methoxy-3α,5-cyclo-5α-pregn-17(20)-en-21-oate (**16**) with lithium diisopropylamide followed by alkyl halides results in the highly predominant formation of Δ^{16}-(20*S*) alkylation products **6a**, **6b**, **14**, and **17** in isolated yields of 82% or higher. Synthetic applications to both 20*S* and 20*R* steroidal side chains are described. Contrary to the conventional rule, 20-H$_\alpha$-Δ^{16}-steroids consistently exhibit the diagnostic C(20) methyl resonance signal at 0.05–0.1 ppm higher than the 20-H$_\beta$-Δ^{16}-steroids. In addition, it was found that stereochemistry at the C(20) position of ethyl 20-alkylpregn-16-en-21-oates could easily be assigned by circular dichroism measurements.

The recent discovery of biologically interesting steroids with modified side chains,[1] such as insect molting hormones (ecdysones),[2] plant anticancer sterols,[3] metabolites of vitamin D,[4] shark repellents,[5] plant growth promoting brassinolides,[6] and marine sterols with "unusual" configurations at C(20),[7] has stimulated the development of

Scheme I



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