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A REGIO- AND STEREOSELECTIVE SYNTHESIS OF METHYL α-L-RISTOSAMINIDE HYDROCHLORIDE

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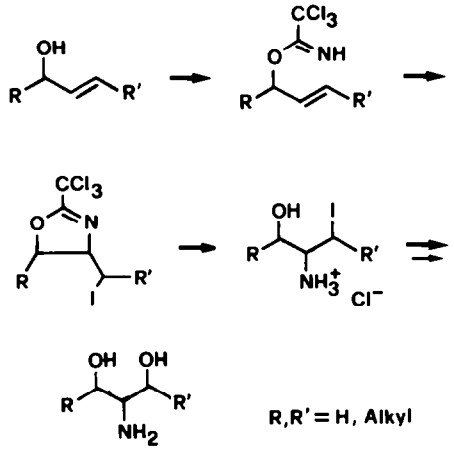
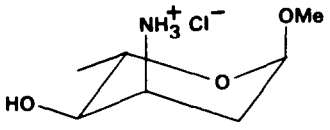
Abstract - Methyl 4-O-trichloroacetimido-2,3,6-trideoxyhex-2-en-α-L-erythropyranoside 3, prepared from methyl 2,3,6-trideoxyhex-2-en-α-L-erythropyranoside 2, underwent a halocyclization reaction to the halooxazoline 4a or 4b, depending on the halonium ion source. By hydrolysis under acidic conditions, 4a and 4b were converted to the corresponding hydrochlorides 5a and 5b, respectively. The dehalogenation reaction, performed with Bu_3SnH, gave methyl 3-amino-2,3,6-trideoxy-α-L-ribopyranoside hydrochloride (methyl α-L-ristosaminide) 1 in very good yield.

In previous papers we described new methods for regio- and stereocontrolled functionalization of double bonds in allylic and homoallylic alcohols. Thus 1,2- and 1,3-diols, epoxyalcohols and triols were synthesized starting from the corresponding iodocarbonates, obtained by treatment of lithium alkoxides with carbon dioxide, followed by iodocyclization [1], while iodoaminoalcohols were obtained via iodo-1,3-oxazolines and iododihydro-1,3-oxazines [2], prepared by iodocyclization of allylic and homoallylic trichloroacetimidates. This latter reaction allowed to introduce 1,2- or 1,3-hydroxyamino and 1,3-dihydroxy-2-amino moieties, which are present in a number of bioactive products, such as the amino sugars [3].



Currently there is considerable interest in developing efficient syntheses of these compounds, because they are the glycosidic residue of a number of anticancer antibiotics [4].

In this area we describe here a regio- and stereoselective synthesis of methyl α-L-ristosaminide hydrochloride 1, the methyl glycoside of ristosamine, 3-amino-2,3,6-trideoxy-L-ribohexose, a component of the antibiotic ristomycin [5].



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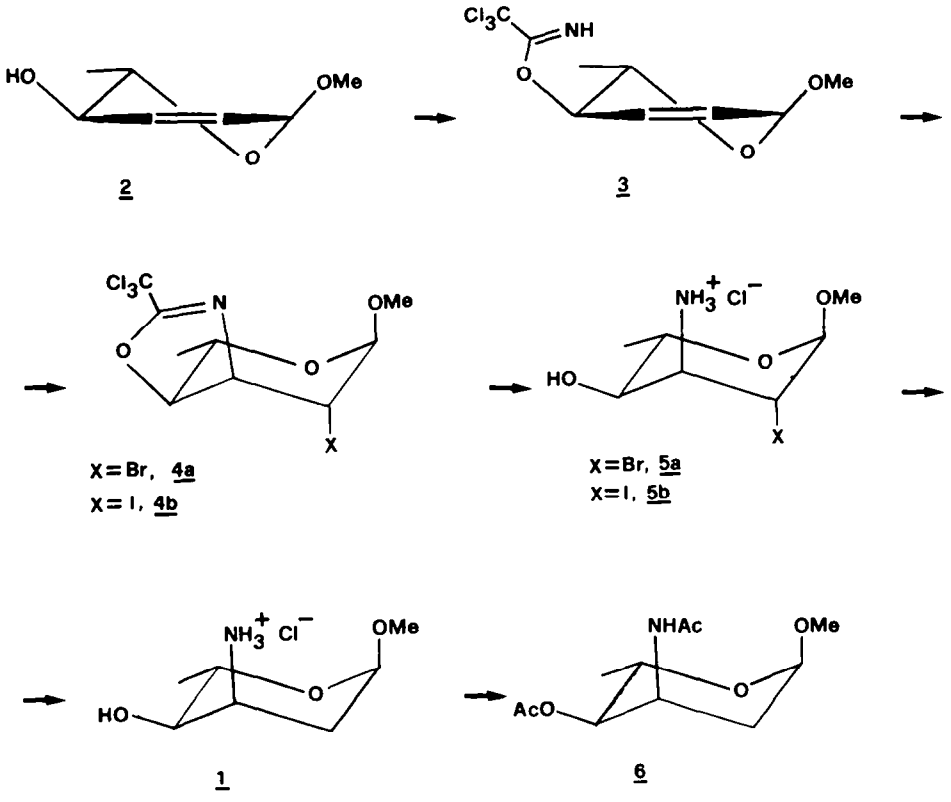
The substrate required for our synthetic approach was methyl 2,3,6-trideoxyhex-2-en-α-L--erythropyranoside 2 [6], whose optical rotation and ^{1}H NMR spectrum were in total agreement with the data reported [7] in the literature. This compound was converted in 88% yield into the trichloroacetimidate 3, by treatment in dry THF with a catalytic amount of NaH and successive addition of the mixture at 0°C to an equimolar solution of trichloroacetonitrile in dry THF [8].

A point of practical interest is the halocyclization of the imidate 3 [7]. We have chosen here to perform the bromocyclization using N-bromosuccinimide in t-butyl alcohol at r.t. for 5 h [9]; this seems to be an advantageous process, since the bromooxazoline 4a was obtained in 95% yield. To avoid aqueous work-up and chromatographic separation of the reaction mixture, which causes cleavage of the

Scheme



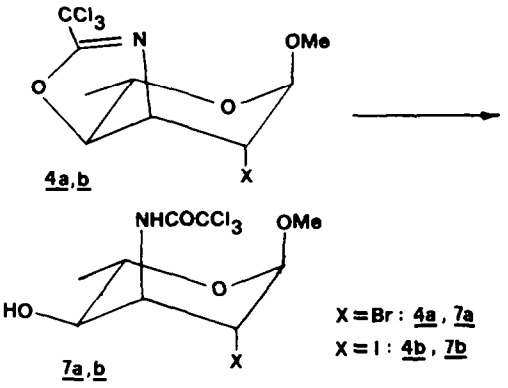
2 3

X=Br, 4a
X=I, 4b

X=Br, 5a
X=I, 5b

1 6

oxazoline ring and formation of the corresponding hydroxyamide 7a, the solvent was evaporated and the residue dissolved in $CHCl_3$: excess bromine and succinimide were eliminated simply by stirring with Amberlyst A 26 (Cl^-) [10].



In analogy, iodocyclization was performed with N-iodosuccinimide in $CHCl_3$ for 4 h at r.t. and yielded the desired iodooxazoline 4b in quantitative yield, free from hydroxyamide 7b, following the previously reported work-up.

In view of the promising results of the halocyclization results, we turned our attention to the hydrolysis [2a] of 4a and 4b which was performed with aqueous HCl in methanol. Under strongly acidic conditions, after 24 h at r.t., the hydrochlorides 5a and 5b were isolated in quantitative yield and no trace of trichloroacetate ion was observed in the ^{13}C NMR spectra.

Cleavage of the C-Br or C-I bonds was performed with 1.5 equiv of Bu_3SnH in refluxing benzene:methanol [1a,11], and methyl α-L-ristosaminide hydrochloride 1 was obtained in 88% yield after silica gel chromatography. The successive acetylation with acetic anhydride : pyridine afforded the corresponding diacetate 6 in 90% yield. On the contrary, when the halooxazolines 4a and 4b were subjected to the dehalogenation reaction with Bu_3SnH, a complex mixture of products was observed, due to the presence of the C-Cl bonds susceptible to cleavage.

This synthesis is characterized by a total regio- and stereoselection. In fact only the oxazolines 4a and 4b were observed in the reaction mixtures and no trace of oxazines was detected. Furthermore a total stereoselection was also shown by ^{13}C NMR analysis of the crude products, since only the peaks corresponding to a single isomer were observed. In conclusion, the method here reported represents a simple regio- and stereoselective route to methyl α-L-ristosaminide hydrochloride 1 [12], and the potential of this approach for general synthesis of 2,3,6-trideoxy-3-aminohexoses in their optically active form is under study.

EXPERIMENTAL

Tetrahydrofuran (THF) was distilled from $LiAlH_4$ or sodium/benzophenone immediately prior to use. All reactions involving organometallic reagents were conducted under argon atmosphere. Melting points (Pyrex capillary) were determined on a Buchi 510 hot stage apparatus and are uncorrected. IR spectra were determined with a Perkin-Elmer Model 682 infrared recording spectrophotometer. ^1H NMR spectra were determined on a Perkin-Elmer R 12 B (60 MHz) spectrometer. ^{13}C NMR spectra were measured at 20 MHz with a Varian FT 80-A spectrometer. Chemical shifts are reported as δ units (ppm) relative to tetramethylsilane (Me_4Si) as an internal reference. Optical rotations were measured with a Perkin-Elmer 241 digital polarimeter at room temperature. Mass spectra were obtained with a double-focusing Varian MAT 112 at an ionizing voltage of 70 eV. Mass spectral data are tabulated as m/e values. Thin-layer chromatography was performed on silica gel

HF_{254} (Merck) and column chromatography on silica gel 60 (Merck, 0.040 - 0.063 mesh).

Methyl 4-O-trichloroacetimido-2,3,6-trideoxy-hex-2-en-α-L-erythropyranoside 3

A solution of 2 (1.44 g; 10 mmol) in dry THF (20 ml) in argon atmosphere was added at 0°C under stirring to a suspension of NaH (50% in mineral oil: 100 mg; 2 mmol; previously washed with dry pentane) in THF (10 ml). After 1 h the resulting mixture was added dropwise to a solution of trichloroacetonitrile (1.6 g; 11 mmol) in dry THF (10 ml). The solution was stirred for 1.5 h and then concentrated under reduced pressure. Pentane (30 ml) containing methanol (1 ml) was added under stirring: successive filtration, evaporation of the solvent and silica gel chromatography of the residue gave 2.5 g (88%) of 3 as a colorless oil; IR (neat): 3340, 1655 cm^{-1}; ^1H NMR ($CDCl_3$): 1.25 (d, 3 H; J = 6 Hz), 3.45 (s, 3 H), 4.15 (dq, 1 H; J = 6 Hz; J = 9.5 Hz), 4.9 (bs, 1 H), 5.2 (bd, 1 H; J = 9.5 Hz), 5.7 - 6.2 (m, 2 H), 8.45 (bs, 1 H, =NH); ^{13}C NMR ($CDCl_3$): 18.0 (C-6), 55.8 (OCH_3), 64.8 (C-5), 75.5 (C-4), 86.2 (CCl_3), 95.6 (C-1), 128.0 (C-3), 128.6 (C-2), 162.0 (C=NH); $\alpha_D^{\bullet}$ = -150.4° (c = 1; CH_2Cl_2); MS (m/e): 244 (M^+ - $CHOCH_3$), 215, 101, 96, 72.

Methyl 2-bromo-2,3,6-trideoxy-4,3(2-trichloromethyl-1-oxa-3-azaprop-2-eno)-α-L-altropyranoside 4a

To a stirred solution of 3 (2.9 g; 10 mmol) in t-butyl alcohol (50 ml), N-bromosuccinimide (2.0 g; 11 mmol) was added at room temperature. After 5 h the solvent was evaporated under vacuum and the residue dissolved in $CHCl_3$ (70 ml). The solution was treated with dried Amberlyst A 26 (Rohm and Haas) (Cl^-) (16 g) to remove bromine and succinimide. The resin was then filtered off and evaporation of the solvent gave 3.45 g of 4a (95%) as a white solid: m.p. 140°C; IR (nujol): 1660 cm^{-1}; ^1H NMR (DMSO-d_6): 1.25 (d, 3 H; J = 6 Hz), 3.3 (s, 3 H), 3.7 - 4.3 (m, 2 H), 4.6 - 4.9 (m, 3 H); ^{13}C NMR (DMSO-d_6): 18.6 (C-6), 48.5 (C-2), 55.1 (OCH_3), 63.4 (C-5), 69.5 (C-3), 84.2 (C-4), 101.1 (C-1), 162.4 (C=N); $\alpha_D^{\bullet}$ = +87.3° (c = 1; CH_2Cl_2); MS (m/e): 365 (M^+), 336, 307, 250, 226, 138, 136, 117.

Methyl 2-iodo-2,3,6-trideoxy-4,3(2-trichloromethyl-1-oxa-3-azaprop-2-eno)-α-L-altropyranoside 4b

To a stirred solution of 3 (2.3 g; 8 mmol) in $CHCl_3$ (80 ml), N-iodosuccinimide (1.9 g; 8.5 mmol) was added at room temperature. After 5 h the reaction mixture was treated with dried Amberlyst A 26 (Rohm and Haas) (Cl^-) (15 g) to remove iodine and succinimide. The resin was then filtered off and evaporation of the solvent gave 4b practically pure in a quantitative yield as a white solid: m.p. 134 - 136°C; IR (nujol): 1650 cm^{-1}; ^1H NMR ($CDCl_3$): 1.4 (d, 3 H; J = 6 Hz), 3.45 (s, 3 H), 3.7 - 4.3 (m, 2 H), 4.4 - 4.9 (m, 2 H), 5.05 (d, 1 H; J = 6 Hz); ^{13}C NMR ($CDCl_3$): 19.1 (C-6), 23.5 (C-2), 55.8 (OCH_3), 63.1 (C-5), 71.4 (C-3), 84.4 (C-4), 86.2 (CCl_3), 103.8 (C-1), 163.4 (C=N); $\alpha_D^{\bullet}$ = +30.8° (c = 1; CH_2Cl_2); MS (m/e): 413 (M^+), 383, 354, 296, 286, 242, 197, 184, 117.

Methyl 2-bromo-3-amino-2,3,6-trideoxy-α-L-altropyranoside hydrochloride 5a

To a stirred solution of 4a (3.65 g; 10 mmol) in methanol (30 ml) at room temperature, 6 N HCl (3 ml) was added. After 24 h the solvent was evaporated and the solid residue washed with ether to give 5a in a quantitative yield as a white solid: m.p. 178°C (dec); ^1H NMR (CD_3OD): 1.35 (d, 3 H; J = 6 Hz), 3.4 (s, 3 H), 3.7 - 4.1 (m, 3 H), 4.35 (m, 1 H), 4.7

(bs, 4 H; OH, NH_3^+), 4.8 (d, 1 H; J = 3 Hz); ^{13}C NMR (DMSO-d_6): 17.2 (C-6), 45.2 (C-2), 53.1 (OCH_3), 54.7 (C-3), 64.9 (C-4), 65.1 (C-5), 98.4 (C-1); α_D° = -41.4° (c = 1; CH_3OH); MS (m/e): 239 (M^+), 208, 182, 164, 116, 99.

Methyl 2-iodo-3-amino-2,3,6-trideoxy-α-L-altropyranoside hydrochloride 5b

To a stirred solution of 4b (4.1 g; 10 mmol) in methanol (30 ml) at room temperature, 6N HCl (3 ml) was added. After 24 h the solvent was evaporated and the solid residue washed with ether to give 5b in a quantitative yield as a white solid: m.p.: 168°C (dec); ^1H NMR (CD_3OD): 1.35 (d, 3 H; J = 6 Hz), 3.4 (s, 3 H), 3.6 - 4.3 (m, 3 H), 4.5 (m, 1 H), 4.8 (bs, 4 H; OH, NH_3^+), 4.9 (d, 1 H; J = 3 Hz); ^{13}C NMR (DMSO-d_6): 17.3 (C-6), 21.2 (C-2), 54.3 (OCH_3), 54.4 (C-3), 64.2 (C-4), 65.1 (C-5), 99.8 (C-1); α_D° = -31.8° (c = 1; CH_3OH); MS (m/e): 256 ($M^+ - OCH_3$), 171, 129, 128, 99.

Methyl 3-amino-2,3,6-trideoxy-α-L-ribopyranoside hydrochloride (methyl α-L-ristosaminide hydrochloride) 1

To a solution of 5a (2.8 g; 10 mmol) and azobisisobutironitrile (1.65 g; 10 mmol) in benzene (30 ml) and methanol (7 ml), tri-n-butyltin hydride (4.3 g; 15 mmol) was added and the mixture refluxed for 6 h. Evaporation of the solvents gave a syrup which was separated on a silica gel column (ethyl acetate:methanol 7:3) to give 1.6 g (88%) of 1 as a white solid; under the same experimental conditions an identical yield was observed for the deiodination of 5b: m.p. 167 - 168°C (Lit. [5a]: 168 - 170°C); ^1H NMR (CD_3OD): 1.2 (d, 3 H; J = 6 Hz), 1.9 (m, 2 H), 3.3 (s, 3 H), 3.5 - 4.3 (m, 3 H), 4.7 (bs, 4 H; OH, NH_3^+), 4.75 (bs, 1 H); ^{13}C NMR (CD_3OD): 18.2 (C-6), 35.1 (C-2), 49.8 (C-3), 55.2 (OCH_3), 64.0 (C-5), 73.7 (C-4), 99.6 (C-1); α_D° = -123.2° (c = 1; CH_3OH) (Lit. [5a]:-123.8°(c = 1; H_2O)); MS (m/e): 161 (M^+), 142, 130, 127, 104, 100, 85, 84, 72.

Methyl 4-O-acetyl-3-acetamido-2,3,6-trideoxy-α-L-ribopyranoside 6

To a stirred solution of 1 (0.9 g; 5 mmol) in pyridine (3 ml), acetic anhydride (2 ml) was added at room temperature and the mixture stirred for 24 h. Pyridine and acetic anhydride were evaporated under vacuum and the residue was purified by column chromatography (ethyl acetate:cyclohexane 8:2) to give 1.1 g (92%) of 6 as a white solid: m.p. 51°C (Lit. [5a]: 51 - 52°C); IR (nujol): 3420, 1740, 1680 cm^{-1}; ^1H NMR ($CDCl_3$): 1.22 (d, 3 H; J = 6 Hz), 1.95 (m, 2 H), 2.0 (s, 6 H), 3.45 (s, 3 H), 4 (dq, 1 H; J = 6 Hz; J = 9 Hz), 4.3 - 4.9 (m, 3 H), 6.85 (d, 1 H; NH; J = 8 Hz); ^{13}C NMR ($CDCl_3$): 17.5 (C-6), 20.9, 23.6 ($\underline{C}H_3CO$), 33.2 (C-2), 43.6 (C-3), 55.2 (OCH_3), 61.7 (C-5), 73.1 (C-4), 98.3 (C-1), 169.8, 170.3 (C=O); α_D° = -130.1° (c = 1, CH_2Cl_2) (Lit. [5a]: -134° (c= 0.5; $CHCl_3$)); MS (m/e): 214 ($M^+ - OCH_3$), 185, 153, 142, 138, 128, 101, 100.

Methyl 2-bromo-3-trichloroacetamido-2,3,6-trideoxy-α-L-altropyranoside 7a

IR (neat): 1690 cm^{-1}; ^1H NMR ($CDCl_3$): 1.4 (d, 3 H; J = 6 Hz), 2.65 (bs, 1 H; OH), 3.45 (s, 3 H), 3.6 - 4.3 (m, 3 H), 4.4 - 4.75 (m, 1 H), 4.85 (d, 1 H; J = 3 Hz), 8.2 (d, 1 H; NH).

Methyl 2-iodo-3-trichloroacetamido-2,3,6-trideoxy-α-L-altropyranoside 7b

IR (neat): 1695 cm^{-1}; ^1H NMR ($CDCl_3$): 1.35 (d, 3 H; J = 6 Hz), 3 (bs, 1 H; OH), 3.45 (s, 3 H), 3.6 - 4.7 (m, 4 H), 4.9 (d, 1 H; J = 2 Hz), 8.25 (d, 1 H; NH)

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REFERENCES AND NOTES

1. (a) G. Cardillo, M. Orena, G. Porzi, S. Sandri, J. Chem. Soc., Chem. Comm., 466 (1981)
   (b) A. Bongini, G. Cardillo, M. Orena, G. Porzi, S. Sandri, J. Org. Chem., 47, 4626 (1982)
2. (a) G. Cardillo, M. Orena, G. Porzi, S. Sandri, J. Chem. Soc., Chem. Comm., 1308 (1982)
   (b) G. Cardillo, M. Orena, G. Porzi, S. Sandri, ibid., 1309 (1982)
3. D. Horton, in " The Amino Sugars " , R. Jeanloz ed., New York, 1969, Vol. IA
4. F. Arcamone, " Doxorubicin. Anticancer Antibiotics " , Academic Press, New York, 1981
5. (a) R. Bognàr, F. Sztaricskai, M. E. Munk, J. Tamàs, J. Org. Chem., 39, 2971 (1974)
   (b) F. Sztaricskai, I. Plyvàs, R. Bognàr, G. Buitàs, Tetr. Letters, 1111 (1975)
   (c) W.W. Lee, H.Y. Wu, J.J. Marsh jr., C.W. Mosher, E.M. Acton, L. Goodman, D.-W. Henry, J. Med. Chem., 18, 767 (1975)
   (d) F. Arcamone, A. Bargiotti, G. Cassinelli, S. Penco, S. Hanessian, Carbohydr. Res., 46, C3 (1976)
   (e) K. Heyns, M. Lim, J.I. Park, Tetr. Letters, 1477 (1976)
   (f) H.H. Baer, F.F.Z. Georges, Carbohydr. Res., 55, 253 (1977)
   (g) I. Pelyvàs, F. Sztaricskai, R. Bognàr, Carbohydr. Res., 76, 257 (1979)
   (h) G. Fronza, C. Fuganti, P. Grasselli, Tetr. Letters, 2999 (1980)
   (i) K. Heyns, J. Feldman, D. Hadamczyk, J. Schwentner, J. Thiem, Chem. Ber., 114, 232 (1981)
   (j) J.S. Brimacombe, R. Hanna, M. Saeed, L.C.N. Tucker, J. Chem. Soc., Perkin I, 2583 (1982)
   (k) C. Fuganti, P. Grasselli, G. Pedrocchi-Fantoni, J. Org. Chem., 48, 909 (1983)
6. R.J. Ferrier, N. Prasad, J. Chem. Soc., (C), 570 (1969)
7. (a) J.S. Brimacombe, L.W. Donner, A.J. Rollins, A.K. Al-Radhi, Tetr. Letters, 87 (1973)
   (b) J.S. Brimacombe, L.W. Donner, A.J. Rollins, J. Chem. Soc., Perkin I, 2977 (1972)
8. (a) L.A. Overman, J. Am. Chem. Soc., 98, 2901 (1976)
   (b) Y. Yamamoto, H. Shimoda, I. Oda, Y. Ynouye, Bull. Chem. Soc. Japan, 49, 3247 (1976)
9. A. Bongini, G. Cardillo, M. Orena, G. Porzi, S. Sandri, Tetr. Letters, 2545 (1979)
10. A. Bongini, G. Cainelli, M. Contento, F. Manescalchi, Synthesis, 143 (1980)
11. D.R. Williams, B.A. Barner, K. Nishitani, J.G. Phillips, J. Am. Chem. Soc., 104, 4708 (1982)
12. After our work had been completed, a publication in this area appeared: H.W. Pauls, B. Fraser-Reid, J. Org. Chem., 48, 1392 (1983)