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A CHIRAL NITRONATE DIANION FROM D-GLYCERALDEHYDE. ENANTIOSPECIFIC SYNTHESES OF 2,3-DIDEOXY-3-NITRO FURANOSIDES AND PYRANOSIDES

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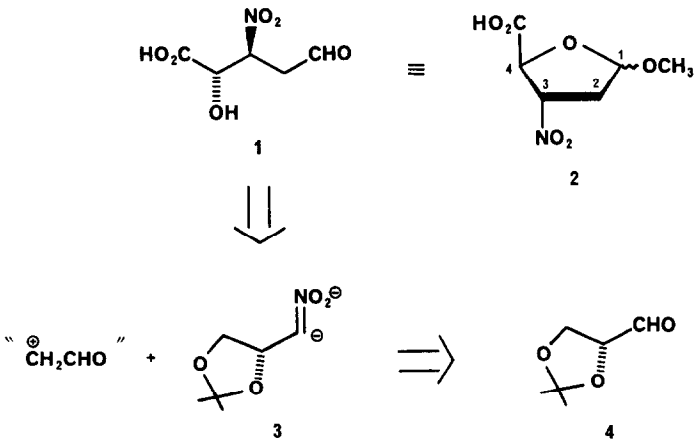
Abstract: A new enantiospecific protocol for the synthesis of 2,3-dideoxy-3-nitro and 3-amino sugars is reported. Chiral nitronate dianion **3**, derived from (+)-D-glyceraldehyde, is allylated and the resulting adduct **7** is transformed to either the methyl furanoside **9** or the methyl pyranoside **10** depending on the reaction sequence.

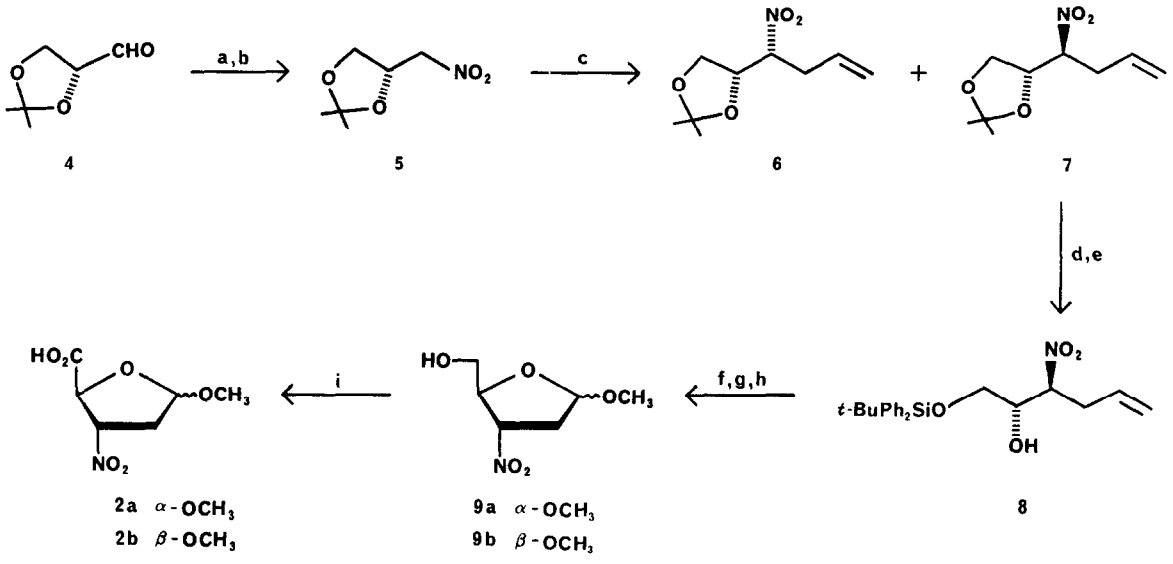
In a previous report[1a] we described the synthesis of the methyl ester of racemic nitrotetrahydrofuranoic acid **2**, a protected form of the five-carbon acid **1** and a synthon in a projected convergent total synthesis of the potent neurotoxin, tetrodotoxin. However a synthesis of chiral **1** (equivalent to **2** with the 2(R),3(S) configuration) was needed for a projected enantiospecific total synthesis of tetrodotoxin[1b].

Scheme I



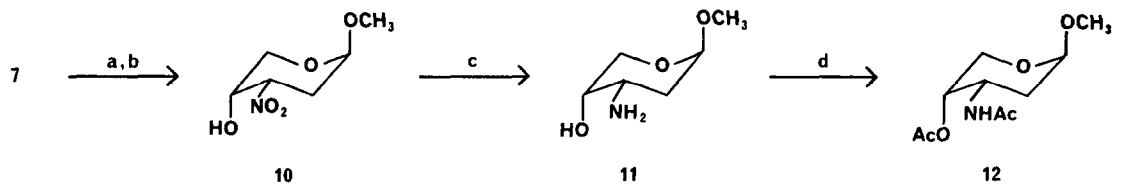
The readily available acetonide of (+)-D-glyceraldehyde **4** was chosen as a convenient starting point[2]. The synthetic strategy depended upon the establishment of the C(3)-C(4) carbon-carbon bond in **2** using the elegant

Scheme II



(a) $NH_2OH \cdot HCl$, pyr, 25°C, 12h, 78%; (b) 6 eq. CF_3CO_3H, Na_2HPO_4, CH_3CN, 0°C, 6h, 86%; (c) i. 2.05 eq. n-BuLi(1.5M in hexane), 9:1 THF/HMPA, -78°C, 3h; ii. $CH_2{=}CHCH_2Br$, -78°C, 2h; iii. HOAc, -78°C, 68% (1:4.5 syn/anti, 70% conversion); (d) 4:1 $HOAc/H_2O$, 40°C, 48h, 100%; (e) t-$BuPh_2SiCl$, imidazole, CH_2Cl_2, 25°C, 30h, 92%; (f) i. O_3, 4:1 CH_2Cl_2/MeOH, pyr, -78°C; ii. Me_2S, -78° to 25°C, 100%; (g) Dowex 50W-X8 (H^+ form), MeOH, 25°-30°C, 19h, 76%; (h) n-Bu_4NF, THF, 25°C, 2.5h, 68%; (i) $RuO_2 \cdot 3H_2O$, $NaIO_4$, CH_3CN, CCl_4, H_2O, 25°C, 4 h, 87%.

Scheme III



(a) i. O_3, 4:1 CH_2Cl_2/MeOH. -78°C; ii. Me_2S, -78° to 25°C, 100%; (b) Dowex 50W-X8 (H^+ form), MeOH, 60°C, 24h, 61% (3:1 β-pyranoside/α,β-furanoside); (c) Raney Nickel, 1 atm H_2, MeOH, 25°C, 4h, 73%; (d) Ac_2O, pyr, $CHCl_3$, 20h, 55%.

nitronate dianion chemistry developed by Seebach[3], using in this case the chiral nitronate dianion **3** (Scheme I). Seebach[4] has investigated lithiated nitronates similar to **3**. Here we describe the generation and use of dianion **3**, a nucleophilic D-glyceraldehyde-derived synthon, for the synthesis of intermediates **6** and **1** with high diastereoselectivity for the S,S (erythro or anti) isomer **1**. The stereochemistry for nitronate dianion chemistry has been discussed in detail including relevant references.[3d,4] It is demonstrated that this is a potentially general protocol for the synthesis of 3-amino-2,3-dideoxy sugars, which are important as moieties of many antibiotics, e.g., daunosamine.[5]

The synthesis of **2** is given in Scheme II. 2,3-O-Isopropylidine-D-glyceraldehyde (**4**)[6] was converted to a mixture of syn- and anti- oximes[7] which were oxidized by the method of Emmons and Pagano[6] to the corresponding nitro compound **5** (bp 62-63°C/0.3mm; $[\alpha]^{20}_D$-17°, c 1.13, $CHCl_3$). Treatment of **5** in 9:1 THF/HMPA at -78°C with 2.05 equiv. of n-BuLi for 3 hours produced dianion **3**, which was alkylated with allyl bromide (-78°C, 2h). Protonation (HOAc, -78°C) of the resulting nitronate gave the syn and anti nitro aldols **6** and **7** in a ratio of 1:4.5 (capillary GC); the possible factors contributing to diastereoselectivity have been discussed.[4] The yields for **6** ($[\alpha]^{20}_D$ -23°, c 1.13, $CHCl_3$) and **7** ($[\alpha]^{20}_D$-7.2°, c 1.40, $CHCl_3$) after flash chromatography[9] were 14% and 54%, respectively, based on recovered **5** (70-85% conversion). The stereochemical assignments in **6** and **7** rest upon the ultimate conversion of **7** to **9a,b**. Ozonolysis of the terminal olefin in **7** gave a quantitative yield of the corresponding aldehyde. Attempts to obtain furanoside **9** by treatment of the aldehyde with acidic methanol, however, were thwarted by concomitant formation of the thermodynamically preferred methyl pyranoside **10**. To circumvent this problem, the acetonide group in **7** was removed with aqueous acetic acid, and the resulting diol was selectively protected using t-butyldiphenylsilyl chloride[10] to give **8** ($[\alpha]^{20}_D$+0.4°, c 1.78, $CHCl_3$). Ozonolysis followed by treatment with acidic methanol gave a mixture of methyl furanosides which, after desilylation, afforded the desired alcohol as a mixture of chromatographically separable anomers (**9a**: $[\alpha]^{20}_D$+142°, c 1.06, CH_3OH, $J_{3,4}$=4.8 Hz; **9b**: $[\alpha]^{20}_D$-104°, c 1.35, CH_3OH,[11] $J_{3,4}$=2.9 Hz). Oxidation of **9a,b** with RuO_4[12] gave the corresponding carboxylic acids (**2a**: $[\alpha]^{20}_D$+155°, c 1.05, CH_3OH, $J_{3,4}$=3.1 Hz; **2b**: $[\alpha]^{20}_D$-86°, c 1.31, CH_3OH, $J_{3,4}$=3.2 Hz).

The stereochemical assignments about the C(3)-C(4) bond of **9a,b**, and **2a,b** (and by inference, the configurations of precursors **6**, **7**, and **8**) are based upon analysis of coupling constants[13]. Chemical evidence for these assignments comes from the conversion of the minor allylation product **6** to the C-3 epimer of **9a**, which upon epimerization with base gives a 5:1 mixture of **9a** ($J_{3,4}$=4.8 Hz) and the C-3 epimer of **9a** ($J_{3,4}$=5.7 Hz). The optical rotations of the α- and β-anomers of **2** and **9** are in accord with Hudson's rules[14].

The thermodynamically preferred methyl pyranoside **10** is also readily

available from nitro aldol **7**. Thus, the crude aldehyde derived from ozonolysis of **7** was refluxed in methanol with Dowex 50W-X8 (H^+ form) to furnish pyranoside **10** (mp 62-64°C, $[\alpha]^{20}_D$-197°, c 1.34, $CHCl_3$). Reduction with Raney nickel gave amino alcohol **11** of high purity; acetylation followed by short column chromatography gave analytically pure acetamide **12** (mp 137-138°C; $[\alpha]^{20}_D$-219°, c 0.60, $CHCl_3$).

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