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DE NOVO-SYNTHESIS OF CARBOHYDRATES– PREPARATION OF 4-AMINO-4-DEOXY-D,L-RIBOSE DERIVATIVES

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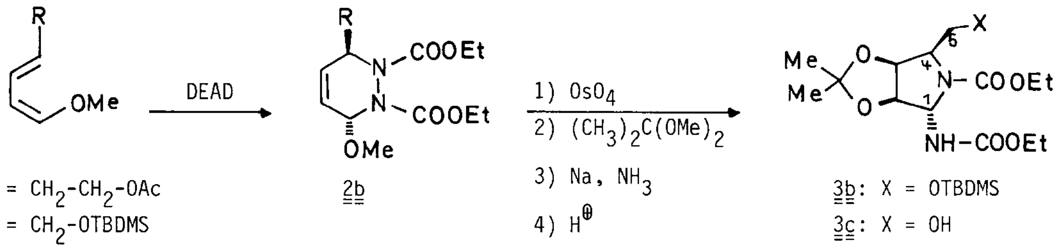
Abstract: *Treatment of 1.2-bis-ethoxycarbonyltetrahydropyridazine 5a with strong base results in ring contraction to the Δ^3-pyrrolines 6a and 7a. The conversion of 6a to ß-D,L-ribo derivatives and 7a to a-D,L-ribo and a-D,L-lyxo derivatives is described.*

Diels-Alder reactions of 1.4-functionally substituted electron rich butadienes with dienophiles and heterodienophiles are a means for the synthesis of cyclitols and carbohydrates and related natural products, respectively [1-3]. The 1-methoxy-4-alkyl-substituted butadiene 1a and glyoxylate as dienophile yielded an efficient thromboxane B_2 synthesis [4], the homologue 1b and diethyl azodicarboxylate (DEAD) yielded adduct 2b, which was easily converted to 4-amino-4-deoxy-D,L-lyxose derivatives 3b-d, as outlined in Scheme 1 [1].

Scheme 1

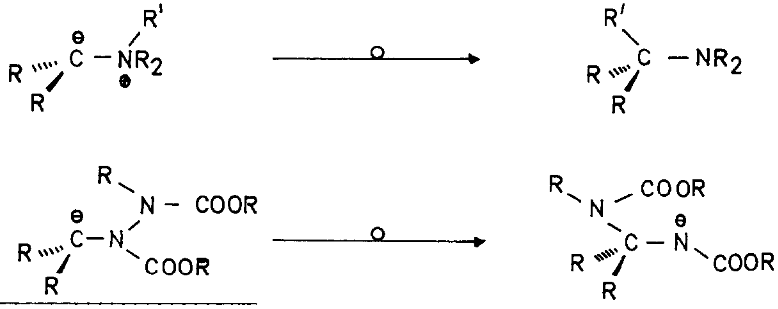


1a: R = CH_2-CH_2-OAc
1b: R = CH_2-OTBDMS

2b

3b: X = OTBDMS
3c: X = OH
3d: X = OAc

Scheme 2



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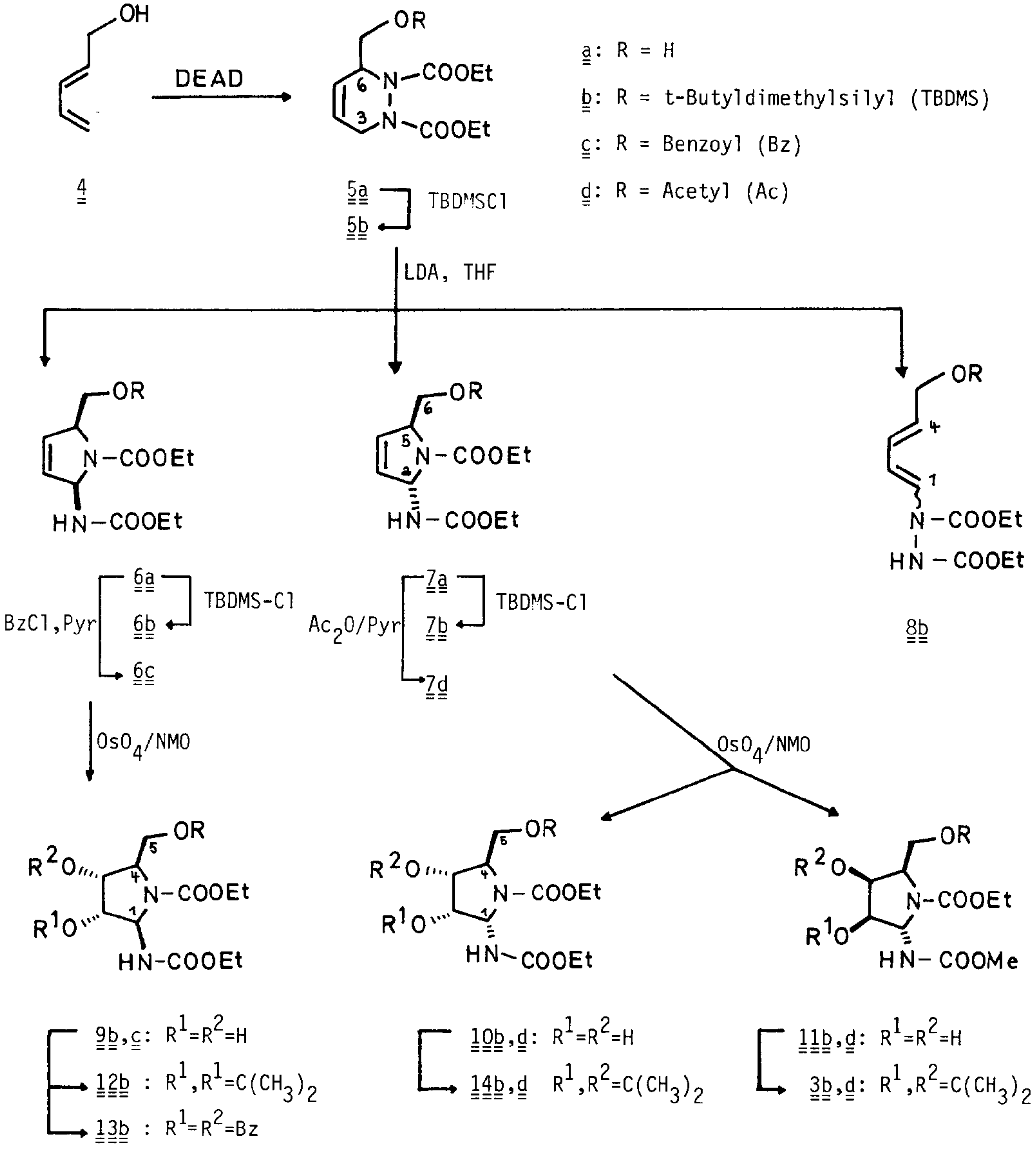
Scheme 3 [a]



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[a] only one enantiomer depicted.

The introduction of a functional group at C-1 of butadiene and the reductive cleavage of the NN-bond (Scheme 1) would not be required, if by cleaving the NN-bond the concomitant oxidation of C-1 of butadiene could be effected. In the Stevens rearrangement nitrogen ylids suffer a [1.2]-sigmatropic carbon shift from nitrogen to carbon (Scheme 2). Therefore, carbanion formation α to a hydrazino or hydroxylamino group could induce the required nitrogen shift from nitrogen to carbon 5), which relates to the Polonovski reaction and to the Wittig and Pummerer rearrangements. However, ease of deprotonation of the α-C-H bond, nucleophilicity of the generated carbanion, steric requirements for the rearrangement, and stabilization of the negative charge in the rearrangement product should be determining factors.

The tetrahydropyridazine **5a**, obtained from pentadienol **4** 6) and DEAD in high yield, seems to be a good substrate for this rearrangement. Treatment of **5a** at -45°C with 2.2 equivalents of lithium diisopropylamide (LDA) gave the expected rearrangement products **6a**, **7a** diastereoselectively (**6a**:**7a** = 4:1, yield 54 %, mp. **6a** 68-71°C; **7a**: 156°C); the yield and product ratio at -70°C was unchanged. **6a** and **7a** were silylated with tert.-butyldimethylsilylchloride to give **6b** (88 %; mp: 57-59°C) and **7b** (93 %; mp: 59-62°C), respectively. Silylation of **5a** to **5b** and treatment with 1.1 equivalents of LDA gave only a 16 % yield of a mixture of **6b** and **7b**. The major product **8b**, which was isolated in 43 % yield, arose from elimination.

Cis-hydroxylation of **6b** using osmiumtetroxide and N-Methylmorpholin-N-oxide (NMO) gave diastereospecifically the ß-N-glycoside of 4-amino-4-deoxy-D,L-ribose derivative **9b** (79 %; mp. 97-98°C). Similarly via benzoylation of **6a** (→**6c**, 74 %; mp. 98-99°C) and cis-hydroxylation the O-benzoyl 4-amino-4-deoxy-D,L-ribose derivative **9c** (94 %, oil) was obtained. Compound **9b** was isopropylidenated with 2.2-diemthoxypropane to give **12b** (56 %; mp. 83°C). Benoylation of **9b** gave the O-benzoyl derivative **13b** (87 %).

Acetylation of compound **7a** yielded the acetate **7d** (90 %, mp: 168-169°C) which was hydroxylated (OsO_4/NMO) to give a 1:1 mixture of the α-D,L-ribo and α-D,L-lyxo derivatives **10d** and **11d** (88 %). Isopropylidenation of the mixture and separation by column chromatography afforded **14d** and **3d** 7). cis-Hydroxylation of **7b** gave **10b** (mp. 127-128°C) and **11b** (oil) in 4:1 ratio (75 % yield). Isopropylidenation of **10b** led to **14b** (oil) in low yield, however, **11b** could not be cleanly isopropylidenated to give **3b** due to the acid lability of the TBDMS group.

The compounds are particularly suited for conversion into nucleoside analogs. For the conversion into methyl O-glycoside the method of Larm was used 8). Treatment of **13b** with N_2O_4 in CH_2Cl_2/pyridine at 0°C gave a rapid and quantitative conversion to the less polar N-nitroso intermediate, which yielded with methanol/pyridine (3 h, reflux) the expected O-glycoside **15** (44 %) 9).

1) De novo-Synthesis of Carbohydrates and Related Natural Products, Part 16. - This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. A Royal Society/SERC Post-Doctoral Fellowship (to A.K. Forrest) is gratefully acknowledged. - For part 15 see: A.K. Forrest, R.R. Schmidt, G. Huttner, and I. Jibril, J.Chem.Soc.Perkin Trans. I, accepted for publication.

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6) M.P. Schneider and M. Goldbach, J.Am.Chem.Soc. **102**, 6114 (1980).

7) The structure of **3d** was assigned by comparison with an acetylation product of an X-ray analyzed compound; see ref. 1, part 15. This gave further support for the structural assignments of compounds **9**-**14**.

8) O. Larm, Carbohydr.Res. **43**, 192 (1975).

9) The isolated products gave satisfactory analytical and spectral data. ^1H NMR (250 MHz, $CDCl_3$, TMS int.): **3d** (60°C): δ 5.6 (br.s, 1H, NH); 5.1-4.9 (m, 3H, 1-H, 2-H, 3-H); 4.7 (dd, 1H, 5-H; J=9.8, 3 Hz); 4.4-4.0 (m, 6H, 4-H, 5'-H, $2O\underline{CH_2}CH_3$); 2.0 (s, 3H, CH_3CO); 1.45, 1.35 (2s, 6H, $C(CH_3)_2$); 1.26, 1.27 (2t, 6H, $2OCH_2\underline{CH_3}$). **6a** (60°C): δ 6.13 (d, 1H, 2-H; J= 9 Hz); 5.83 (m, 2H, 3-H and 4-H); 5.10 (br.s, 1H, NH); 4.58 (m, 1H, 5-H); 4.0-4.3 (m, 4H, $2O\underline{CH_2}$-CH_3); 3.95 (br.d, 1H, 6-H; J=11 Hz); 3.62 (br.d, 1H, 6'-H; J=11 Hz); 2.75 (s, 1H, OH); 1.27, 1.24 (2t, 6H, $2OCH_2\underline{CH_3}$). **6b** (60°C): δ 6.10 (d, 1H, 2-H; J=9.5 Hz); 5.80 (2d, 2H, 3-H and 4-H; J=6.1 Hz); 5.0 (br.s, 1H, NH); 4.5 (br.s, 1H, 5-H); 4.2 (m, 4H, $2O\underline{CH_2}CH_3$); 3.95, 3.60 (2d, 2H, 6-H and 6'H; J=10.1 Hz), 1.2 (2t, 6H, $2OCH_2\underline{CH_3}$); 0.9 (s, 9H, $C(CH_3)_3$); 0.07 (s, 6H, $Si(CH_3)_2$). **7a** (60°C): δ 6.2 (ddd, 1H, 2-H; J=9.4, 3.05, 1.5 Hz); 5.85 (ddd, 1H, 3-H; J=6.5, 1.6, 1.5 Hz); 5.75 (dm, 1H, 4-H; J=6.5 Hz); 4.7 (br.m, 2H, 5-H, NH); 4.2 (m, 4H, $2O\underline{CH_2}CH_3$), 3.8, 3.6 (2m, 2H, 6-H, 6'-H); 1.25 (2t, 6H, $2OCH_2\underline{CH_3}$). **7b** (60°C): δ 6.1 (br.s, 1H, 2-H); 6.0 (ddd, 1H, 3-H or 4-H; J=6.0, 1.8, 1.5 Hz); 5.7 (br.d, 1H, 4-H or 3-H; J=6.0 Hz); 4.75 (m, 1H); 4.55 (br.s, 1H); 4.1 (m, 4H, $2O\underline{CH_2}$-CH_3); 3.96 (dd, 1H, 6-H; J=9.8, 2.9 Hz); 3.7 (m, 1H, 6'-H); 1.25 (t, 6H, $2OCH_2\underline{CH_3}$); 0.9 (s, 9H, $C(CH_3)_3$); 0.02, 0.01 (2s, 6H, $Si(CH_3)_2$). **7d** (60°C): δ 6.1 (br.s, 1H, 2-H); 5.9, 5.8 (2d, 2H, 3-H, 4-H; J= 6.5Hz); 4.8 (br.s, 1H, NH); 4.7 (br.s, 1H, 5-H); 4.45 (dd, 1H, 6-H; J=11, 2 Hz); 4.4-4.0 (m, 5H, 6'-H, $2O\underline{CH_2}CH_3$); 2.0 (s, 3H, $COCH_3$); 1.26, 1.24 (2t, 6H, $2OCH_2\underline{CH_3}$). **8b** (60 MHz, r.t.): δ 7.15 (br.s, 1H, NH), 6.65 (d, 1H, 1-H; J=10 Hz); 6.57 (dd, 1H, 3-H; J=10, 10 Hz); 5.85-5.45 (m, 2H, 2-H, 4-H); 4.40 (d, 2H, 5-H, 5'-H; J=5 Hz); 4.30, 4.28 (2q, 4H, $2O\underline{CH_2}$-CH_3; J=7 Hz); 1.28, 1.25 (2t, 6H, $2OCH_2\underline{CH_3}$); 0.9 (s, 9H, $C(CH_3)_3$); 0.05 (s, 6H, $Si(CH_3)_2$). **9b** (r.t.): δ 5.5 (br.m, 2H); 4.3 (br.s, 1H); 4.1 (m, 6H); 3.8 (m, 3H); 3.1 (br.s, 1H, OH); 1.25 (m, 6H, $2OCH_2\underline{CH_3}$); 0.9 (s, 9H, $C(CH_3)_3$); 0.1 (s, 6H, $Si(CH_3)_2$). **10b** (r.t.): δ 5.6 (br.m, 1H); 5.25 (br.m, 1H); 4.4 (br.s, 1H); 4.2 (m, 5H); 3.8 (m, 3H); 2.8 (br.s, 2H, 2OH); 1.25 (m, 6H, $2OCH_2$-$\underline{CH_3}$); 0.9 (s, 9H, $C(CH_3)_3$); 0.03, 0.02 (2s, 6H, $Si(CH_3)_2$). **12b** (60°C): δ 5.75 (br.s, 1H, NH); 5.70 (d, 1H; J=8.5 Hz); 4.7 (dd, 1H; J=5.8, 0.9 Hz); 4.45 (d, 1H; J=5.8 Hz); 4.1 (m, 5H); 4.0 (br.m, 1H); 3.75 (dd, 1H; 6-H; J=10.6, 2.0 Hz); 1.4, 1.3 (2s, 6H, $C(CH_3)_2$); 1.2 (t, 6H, $2OCH_2\underline{CH_3}$); 0.9 (s, 9H, $C(CH_3)_3$); 0.14, 0.13 (2s, 6H, $Si(CH_3)_2$). **13b** (60°C): δ 8.0-7.8, 7.6-7.2 (m, 10 H, $2C_6H_5$); 5.9-5.8 (m, 2H, 1-H, 2-H or 3-H); 5.65 (dd, 1H, 3-H or 2-H; J=8 Hz); 5.45 (br.d, 1H, NH; J=8 Hz); 4.3-4.1 (m, 6H, 4-H, 5-H, 2 $O\underline{CH_2}$-CH_3); 3.85 (dd, 1H, 5'-H; J=11, 2 Hz); 1.27, 1.24 (2t, 6H, $2OCH_2\underline{CH_3}$); 1.0 (s, 9H, $C(CH_3)_3$); 0.19, 0.17 (2s, 6H, $Si(CH_3)_2$). **14b** (r.t.): δ 5.7 (br.m, 1H); 5.1 (br.m, 1H); 4.6 (br.s, 2H); 4.1 (m, 6H), 3.6 (d, 1H, J=10 Hz); 1.53, 1.37 (2s, 6H, $2C(CH_3)_2$); 1.28, 1.23 (2t, 6H, $2OCH_2\underline{CH_3}$); 0.9 (s, 5H, $C(CH_3)_3$); 0.05 (s, 6H, $Si(CH_3)_2$). **14d** (60°C): δ 5.6 (dd, 1H, 1-H; J=10, 5.5 Hz); 5.1 (br.d, 1H, NH; J=10 Hz); 4.65 (dd, 1H, 2-H; J=6, 5.5 Hz); 4.55 (d, 1H, 3-H; J=6 Hz); 4.4 (dd, 1H, 5-H; J=10.2, 3.7 Hz); 4.4-4.0 (m, 6H, 4-H, 5'-H, $2O\underline{CH_2}CH_3$); 2.07 (s, 3H, CH_3CO); 1.52, 1.36 (2s, 6H, $C(CH_3)_2$); 1.26, 1.23 (2t, 6H, $2OCH_2\underline{CH_3}$). **15** (60°C): δ 8.0-7.2 (m, 10H, $2C_6H_5$); 5.9 (dd, 1H, 3-H; J=6, 4.5 Hz); 5.6 (dd, 1H, 2-H; J=4.5, 1.2 Hz); 5.3 (br.s, 1H, 1-H); 4.2 (m, 3H, $O\underline{CH_2}$-CH_3, 4-H); 4.0 (dd, 1H, 5-H; J=10.4, 3.6 Hz); 3.95 (dd, 1H, 5'-H; J=10.4, 6.1 Hz); 3.45 (s, 3H, OCH_3); 1.3 (t, 3H, $OCH_2\underline{CH_3}$); 0.86 (s, 9H, $C(CH_3)_3$); 0.05, 0.04 (2s, 6H, $Si(CH_3)_2$).

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