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L-RIBULOSE : A NOVEL CHIRAL POOL COMPOUND

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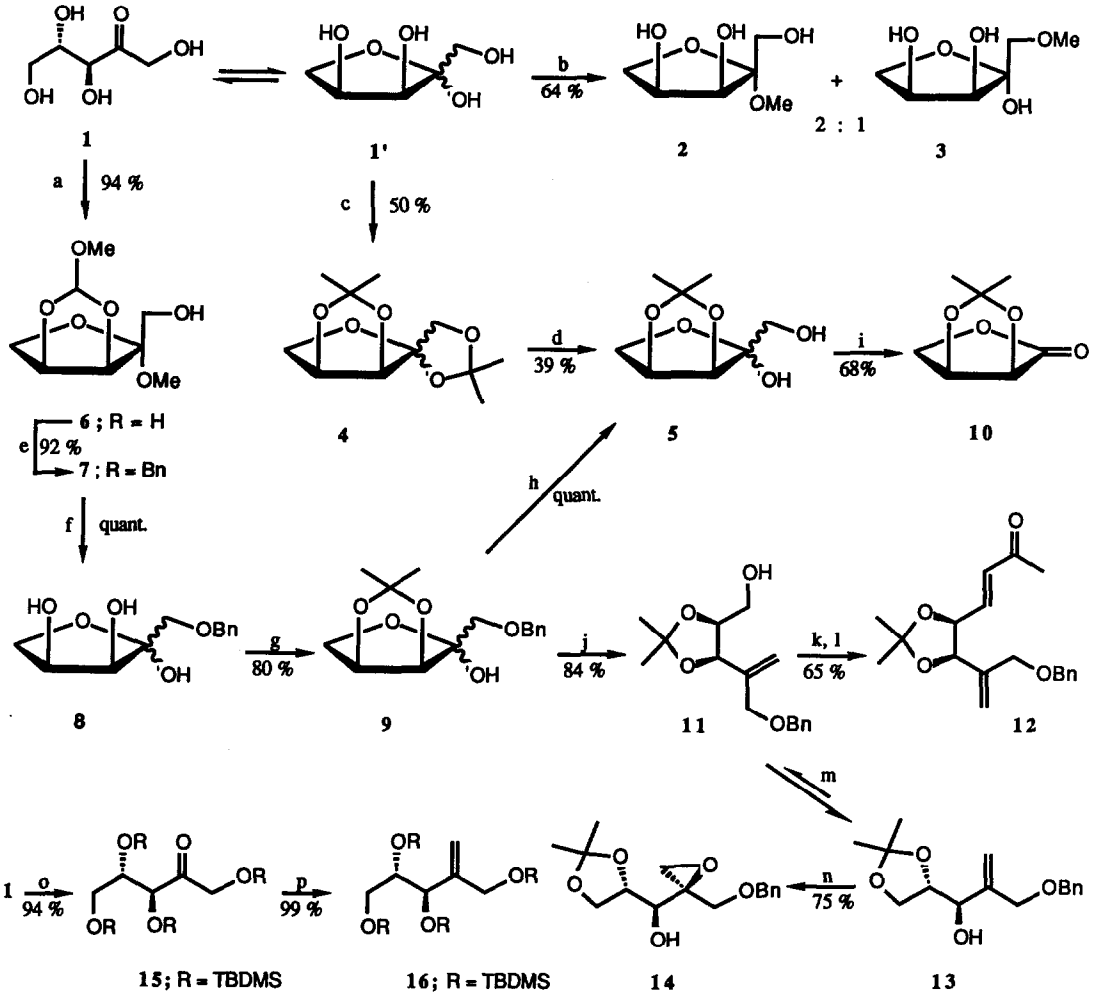
Abstract : *The unnatural keto-sugar L-ribulose, presently more readily available, is an interesting "chiral pool" product. Some key-intermediates for its transformation are described.*

Future developments in the now well-established chiron approach for the total synthesis of natural products is highly dependent upon the availability of optically pure chiral substances[3]. Among the sugar-derived C_5-aldoses and ketoses, L-ribulose (**1**) has now become available in larger quantities[4]. The success of a natural product as a template is related to the ease with which its different functional groups can be selectively manipulated.

In this letter we want to describe the transformation of **1** into a number of derivatives which opens the scope for eventual applications. Of prime importance is the selective protection of the different hydroxyl groups and the keto function (acyclic structure) or anomeric hydroxyl function (furanoside form). Literature data are scarce; two reports respectively describe the non-selective formation of the β- and α-anomeric methyl ethers[5,6] **2** and **3** and the low-efficient formation of the acetonide[6,7] **5** via hydrolysis of the bis-acetonide **4** (Scheme 1).

Reinvestigation of the sequence **1** → **4** → **5** met with little success and convinced us of its unpracticability in any starting sequence. In contrast, orthoester formation with concomitant methoxylation at the anomeric position turned out to be very promising as key-feature for potential applications of **1**. The β-anomer is formed exclusively; **6** occurs as a mixture (4.2:1) of two epimers at the orthoester site. The configuration at the anomeric position in **6** was proven by its transformation into **2**[8] upon selective orthoester hydrolysis, (i : HOAc, 80 %, , r.t., 10 min; ii. NH_4OH, 28 %, r.t., 15 min).

The 1-hydroxyl group in key-intermediate **6** can now selectively be transformed; e.g. formation of the benzyl ether **7**. After acid hydrolysis of **7**, the isopropylidene protected compound **9** could be adequatly obtained. Intermediate **9** is ideally suited for reactions at the crypto-carbonyl function. Hydrogenolysis of the benzyl ether and subsequent oxidative cleavage afforded 2,3-O-isopropylidene-L-erythrono-1,4-lactone **10**[9] in a high overall yield (47 %) compared to the previous described route[7] via **4** (13 %). The crystalline **10** is an optically active derivative of meso-tartaric acid and a valuable template in the total synthesis of natural products. On the other hand, Wittig reaction of **9** leads to **11** in 84 % yield next to 7 % starting material. The free hydroxyl group in **11** allows chain extension; e.g. Dess-Martin oxidation[10] and Horner-Wittig reaction provides **12**, a potential intermediate for the total synthesis of pseudomonic acids[11].

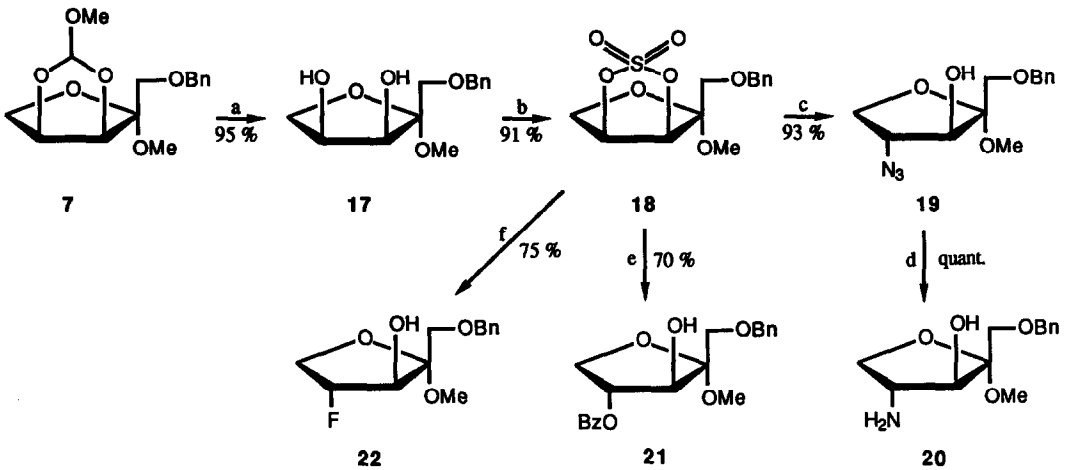


a) $HC(OMe)_3$, MeOH, pTSA, r.t., 24 h; b) MeOH, pTSA, r.t., 2 h; c) $(CH_3)_2C(OMe)_2$, pTSA, r.t., 12 h; d) HOAc:H_2O (4:1), 65°C, 2 h; e) BnBr, KOtBu, THF, r.t., 2 h; f) HCl (10 %), THF, r.t., 4 h; g) $(CH_3)_2C(OMe)_2$, pTSA, r.t., 30 min; h) H_2 (1 bar), Pd-C (10 %), EtOAc, r.t., 6 h; i) $NaIO_4$, H_20, 0°C, 1 h; j) $Ø_3P{=}CH_2$ (3 eq.), THF, 12-crown-4 (0.2 eq.), -60°C → r.t., 4 h; k) Dess-Martin periodinane,[10] CH_2Cl_2, r.t., 30 min, l) $Ø_3P{=}CHCOMe$, CH_2Cl_2, r.t., 2 h; m) acetone, Amberlyst-15, r.t., 12 h; n) $VO(acac)_2$, tBuOOH, CH_2Cl_2, r.t., 4 h; o) TBDMSCl, imidazole, CH_2Cl_2, r.t., 4 h; p) $Ø_3P{=}CH_2$, THF, r.t., 30 min.

Scheme 1

Of interest is the acid mediated equilibration of **11** to **13**. The mixture (ratio 1:6 in favour of **13**) can be separated by preparative HPLC. In **13**, the stereogenic allylic alcohol function allows formation of a new chiral center at C-2. Epoxidation with $VO(acac)_2$-t.BuOOH[11] leads to **14**[9] as a single diastereoisomer (d.e. >95 % as deduced from ^1H NMR analysis). Structure assignment of **14** is based on the Sharpless model[12] and on the formation of **14** in the asymmetric epoxidation involving (+)-diethyl tartrate[13].

As it is normally difficult to protect all alcohol functions of a carbohydrate in the acyclic form (e.g. formation of a mixture of tetra acetates of **1** and **1'**) it is worthwhile to note that the use of the bulky TBDMS group allows high yield formation of the crystalline compound **15**, which was transformed into alkene **16**.



a) HOAc (80 %), r.t., 10 min then NH_4OH (28 %), r.t., 15 min; b) i. $SOCl_2$, NEt_3, CCl_4, 0°C, 10 min; ii. $RuCl_3.3H_2O$, $NaIO_4$, CCl_4, CH_3CN, H_2O, 0°C, 60 min; c) NaN_3, DMF, 80°C, 3 h then THF, H_2O (1 eq.), H_2SO_4 (1 eq.), r.t., 10 min then $NaHCO_3$ (s), r.t., 20 min; d) H_2 (1 bar), Pd-C (10 %), MeOH, r.t., 2 h; e) $ØCO_2NH_4$, DMF, 80°C, 24 h then THF, H_2O (1 eq.), H_2SO_4 (1 eq.), r.t., 30 min then $NaHCO_3$ (s), r.t., 20 min; f) TBAF, DMF, 80°C, 6 h, work up see c).

Scheme 2

The versatility of key-intermediate **7** is furthermore illustrated by the possibility for selective hydrolysis of the orthoester moiety upon mild acid treatment, and subsequent saponification of the intermediate monoformate (Scheme 2). In contrast to reaction f in scheme 1 this allows the formation of intermediate **17**[9] in which the keto function of **1** is still protected. The diol **17** can easily be transformed via the cyclic sulfite into the cyclic sulfate **18**[9] following the improved procedure of Gao and Sharpless[14]. Compound **18**, which is obtained from L-ribulose in 75 % overall yield, is an interesting and highly potential intermediate. Nucleophilic ring opening of the cyclic sulfate **18** occurs, due to steric hindrance at C-3, exclusively at the C-4 position. Azido-opening and subsequent catalytic hydrogenation leads in high yield to the 4-aminosugar **20**; reaction with an oxygen nucleophile affords a protected derivative **21**[9] (70 % + 17 % of **18**) of scarcely available D-xylulose. On the other hand, reaction with fluoride anion (TBAF, DMF) yields the fluoro-derivative **22**[9] as a crystalline compound.

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References and notes

1. Aspirant of the Belgian National Fund for Scientific Research.
2. Research fellow of the Belgian National Fund for Scientific Research. Present address : Agfa-Gevaert, Septestraat, 27, B-2510 Mortsel (Belgium).
3. See for example : Hanessian, S.; Total synthesis of natural products : the "chiron" approach, Pergamon Press, Oxford, 1983.
4. Recently available from Aldrich Chemicals.
5. Stankovic, L.; Linek, K.; Fedoronko, M.; Carbohydr. Res.**1973**, *35*, 242.
6. Reactions originally described on D-ribulose.
7. Tipson, R.S.; Brady Jr., R.F.; Carbohydr. Res.**1969**, *10*, 549.
8. The optical rotation for the triacetate of **2** is $[\alpha]_D^{20}$ = +71.23° (c = 1.49; acetone). The value given in ref. 7 for its enantiomer is, $[\alpha]_D^{25}$ = -56.1° (c = 1; acetone).
9. Physical and spectral data for representative compounds.
   10 : $[\alpha]_D^{20}$ = +116.3° (c = 1.49; acetone), ent **10**, $[\alpha]_D^{25}$ = -111.9° (c = 2.2; acetone).[7] m.p. = +69°C; ^{1}H NMR δ (acetone-d_6) 1.34 (3H, s), 1.38 (3H, s), 4.34 (1H, d, J = 10.85 Hz), 4.49 (1H, dd, J = 3.90, 10.85 Hz), 4.85 (1H, d, J = 5.58 Hz), 5.0 (1H, dd, J = 3.90, 5.58 Hz); HRMS calcd. for $C_7H_{11}O_4$ (MH^+) 159.0657, found 159.0654.
   14 : $[\alpha]_D^{26}$ = +2.0° (c = 1.49; $CHCl_3$), $[\alpha]_{365}^{26}$ = +2.74° (c = 1.49; $CHCl_3$); ^{1}H NMR δ (C_6D_6) 1.25 (3H, s), 1.35 (3H, s), 2.33 (1H, s), 2.37 (1H, d, J = 4.88), 2.65 (1H, d, J = 4.88), 3.46 (1H, d, J = 11.12), 3.72 (1H, d, J = 11.12), 3.86 (1H, ddd, J = 5.87, 6.10, 7.32 Hz), 3.98 (1H, d, J = 7.32 Hz), 3.98 (1H, dd, J = 6.10, 8.65 Hz), 4.08 (1H, dd, J = 5.87, 8.65 Hz), 4.31 (2H, s), 7.14 (5H, m); HRMS calcd. for $C_{15}H_{19}O_5$ (M^+-CH_3O) 279.1230, found 279.1232.
   17 : $[\alpha]_D^{21}$ = +35.79° (c = 1.71; $CHCl_3$), $[\alpha]_{365}^{21}$ = +101.58° (c = 1.71; $CHCl_3$); ^{1}H NMR δ ($CDCl_3$) 3.15 (1H, d, J = 6.47 Hz), 3.21 (1H, s), 3.24 (3H, s), 3.63 (1H, d, J = 10.13 Hz), 3.73 (1H, d, J = 10.13 Hz), 3.87 (1H, dd, J = 2.52, 9.89 Hz), 3.99 (1H, dd, J = 9.89, 4.41 Hz), 4.14 (1H, dd, J = 5.40, 6.47 Hz), 4.30 (1H, ddd, J = 2.52, 4.41, 5.40 Hz), 4.57 (1H, d, J = 11.74 Hz), 4.63 (1H, d, J = 11.74 Hz), 7.35 (5H, m); HRMS calcd. for $C_{12}H_{15}O_4$ ($M^{+\cdot}$-CH_3O) 223.0970, found 223.0966.
   18 : $[\alpha]_D^{26}$ = +62.24° (c = 2.71; $CHCl_3$), $[\alpha]_{365}^{26}$ = +179.20° (c = 2.71; $CHCl_3$); ^{1}H NMR δ (C_6D_6) 2.78 (3H, s), 3.04 (1H, dd, J = 4.13, 11.68 Hz), 3.50 (1H, d, J = 11.68 Hz), 3.51 (1H, d, J = 11.07 Hz), 3.57 (1H, d, J = 11.07 Hz), 4.24 (1H, dd, J = 4.13, 6.14 Hz), 4.08 (1H, d, 11.92 Hz), 4.27 (1H, d, 11.92 Hz), 4.67 (1H, d, J = 6.14 Hz), 7.12 (5H, m); HRMS calcd. for $C_{13}H_{16}O_7S$ ($M^{+\cdot}$) 316.0615, found 316.0614.
   21 : $[\alpha]_D^{26}$ = -2.1° (c = 2.38; $CHCl_3$), $[\alpha]_{365}^{26}$ = -20.6° (c = 2.38; $CHCl_3$); ^{1}H NMR δ (C_6D_6) 3.10 (1H, s), 3.29 (3H, s), 3.67 (1H, d, J = 10.53 Hz), 3.80 (1H, d, J = 10.53 Hz), 3.86 (1H, dd, J = 9.90, 5.18 Hz), 4.52 (1H, dd, J = 6.85, 9.90 Hz), 4.63 (2H, s), 5.22 (1H, ddd, J = 2.00, 5.18, 6.85 Hz), 7.32 (6H, m), 7.57 (1H, m), 8.05 (2H, m); HRMS calcd. for $C_{19}H_{19}O_5$ ($M^{+\cdot}$-CH_3O) 327.1230, found 327.1222.
   22 : $[\alpha]_D^{26}$ = +33.73° (c = 1.49; $CHCl_3$), $[\alpha]_{365}^{26}$ = +96.91° (c = 1.49; $CHCl_3$), m.p. = +58°C; ^{1}H NMR δ (C_6D_6) 2.80 (1H, d, J = 3.58 Hz), 3.09 (3H, s), 3.55 (1H, d, J = 10.65), 3.63 (1H, d, J = 10.65 Hz), 3.80 (1H, ddd, J = 3.28, 10.60, 24.87 Hz), 3.94 (1H, ddd, J = 5.65, 10.60, 24.89 Hz), 4.17 (2H, s), 4.50 (1H, ddd, J = 1.23, 3.58, 15.85 Hz), 4.79 (1H, dddd, J = 1.23, 3.28, 5.65, 53.71 Hz), 7.11 (5H, m); HRMS calcd. for $C_{12}H_{14}FO_3$ ($M^{+\cdot}$-CH_3O) 225.0927, found 225.0929.
10. Dess, D.B.; Martin, J.C.; J. Org. Chem., **1983**, *38*, 4155.
11. (a) : Clayton, J.P.; O'Hanlon, P.J.; Rogers, N.H.; King, T.J.; J. Chem. Soc., Perkin Trans I, **1982**, 2827; (b) : O'Hanlon, P.J.; Rogers, N.J.; Tyler, J.W.; J. Chem. Soc., Perkin Trans I, **1983**, 2655.
12. (a) : Sharpless, K.B.; Verhoeven, T.R.; Aldrichimica Acta, Vol. 12, No. 4, 63 (1979); (b) for an analogous example see Depezay, J.C.; Duréault, A.; Tetrahedron Letters, **1978**, *32*, 2869..
13. Gao, Y.; Hanson, R.M.; Klunder, J.M.; Ko, S.Y.; Masamune, H., Sharpless, K.B.; J. Am. Chem. Soc., **1987**, *109*, 5765.
14. Gao, Y.; Sharpless, K.B.; J. Am. Chem. Soc., **1988**, *110*, 7538.

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