Tetrahedron Letters, Vol. 34, No. 15, pp. 2453-2456, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

1,3-Dioxan-5-one as C_3-Building Block for the Diastereo- and Enantioselective Synthesis of C_5- to C_9-Deoxy Sugars Using the SAMP-/RAMP-Hydrazone Method

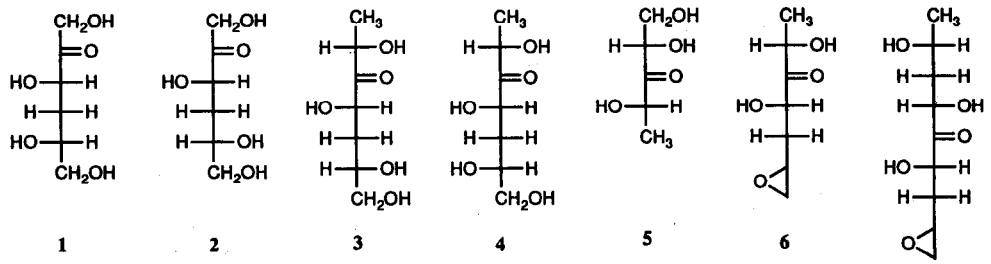
D. Enders*, U. Jegelka

Institut für Organische Chemie, Rheinisch-Westfälische Technische Hochschule, Professor-Pirlet-Straße 1, D-5100 Aachen, Germany.

Abstract: *The diastereo- and enantioselective synthesis of deoxy- and dideoxysugars is demonstrated using the protected dihydroxyacetone derivative 8 as a C_3-building block in combination with the SAMP-/RAMP-hydrazone method.*

The antibiotic and cytostatic activity of carbohydrates is well known[1], as well as the fact that the transformation of healthy cells to cancer cells is accompanied by a significant change in the carbohydrate structure on the cell surface[2]. Antibiotics, such as Rifamycin S[3], Amphotericin B[4] and Palytoxin[5], containing various deoxysugar fragments have recently been isolated and synthesized. In addition deoxysugars have recently been found to play an important role not only in cell-adhesion processes such as the inflammatory response in infections, but also in the reperfusion tissue injuries that often occur after organ transplants[6]. Furthermore, it has recently been demonstrated that these deoxysugars are located on various cancer cells suggesting that they also play an important role in the metastasis of human cancer[7]. Thus the urgency for efficient diastereo- and enantioselective *de novo*-syntheses of deoxysugars for the use as anti-inflammatory or antitumor drugs is increasingly high[8].

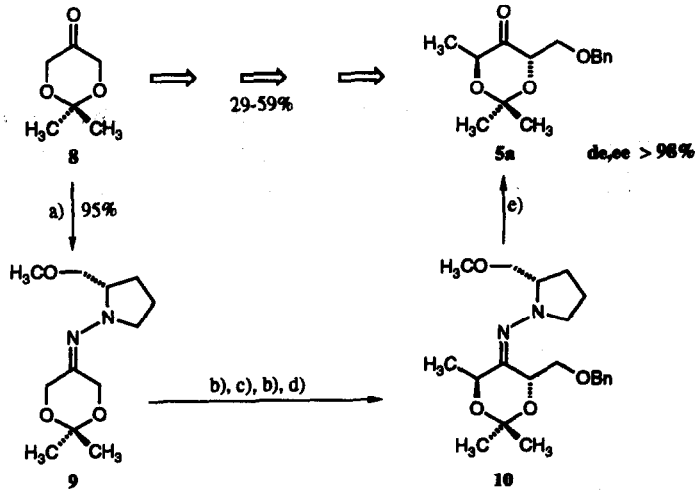
We recently reported the asymmetric synthesis of α,α'-disubstituted, C_2-symmetric ketones by using alkyl halides as electrophiles in SAMP/-RAMP-hydrazone alkylations[9]. Starting from readily available 1,3-dioxan-5-one (**8**)[10], we have now extended this highly stereoselective α,α'-double alkylation technique to the synthesis of C_5-, C_6-, C_7- and C_9-derivatives of the natural and unnatural ketoses **1-7**. In addition, a method to synthesize the corresponding polyols is described.



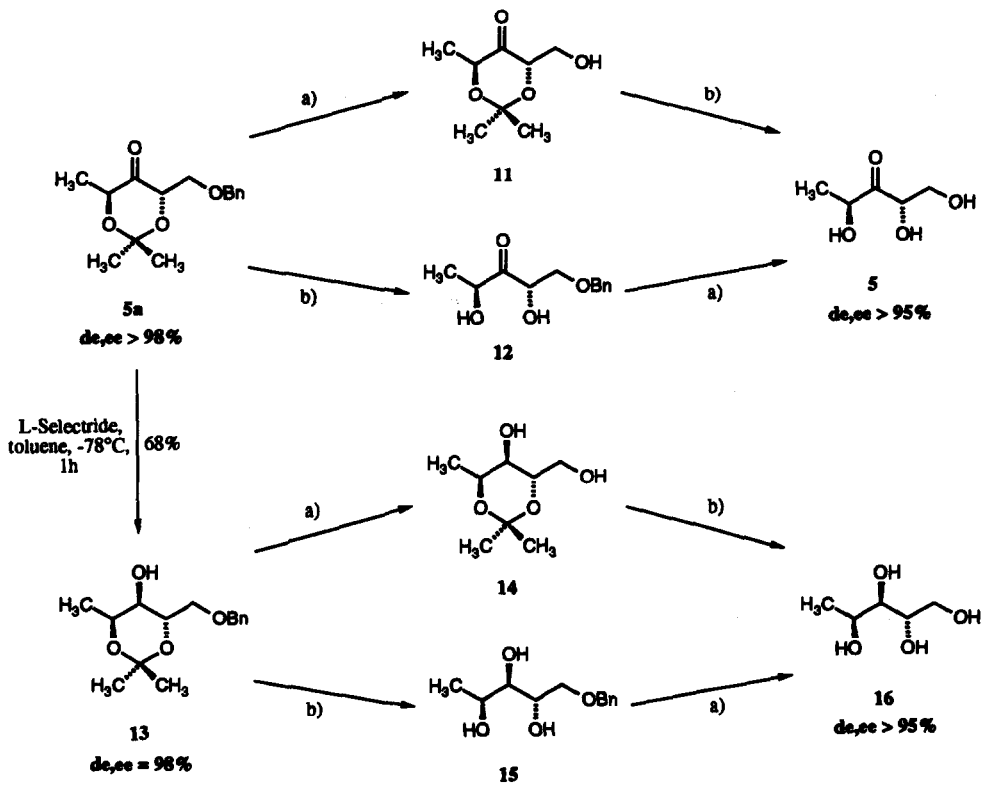
1 **2** **3** **4** **5** **6** **7**

4-Deoxy-L(-)-sorbose | 1,5-Dideoxy-D(-)-*xylo*-3-heptulose | 5-Deoxy-L(-)-*threo*-3-pentulose | 1,2-Anhydro-3,9-dideoxy-D-*gulo*-5-nonulose

4-Deoxy-D(-)-fructose | 1,5-Dideoxy-L-*arabino*-3-heptulose | 6,7-Anhydro- 1,5-dideoxy-L-*arabino*-3-heptulose

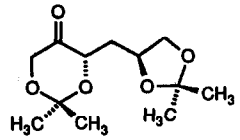
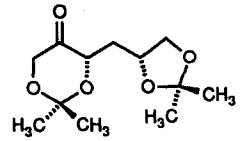
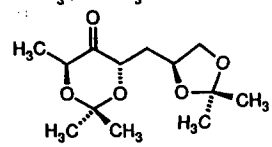
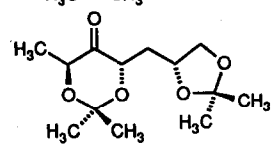
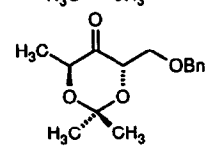
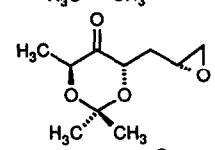
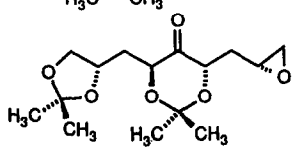


Scheme 1. a) 1 equiv. SAMP, toluene, 110°C, 20h; b) 1.1 equiv. *t*-BuLi, THF, -78°C, 1.5h; c) 1.1 equiv. MeI, -95°C, 1h; d) 1.1 equiv. $ClCH_2OBn$, -95°C, 1h; e) O_3, CH_2Cl_2, -78°C.



Scheme 2. a) H_2, Pd-C (10%), MeOH, 1h, >95%; b) 3N HCl, MeOH, 0.5h, >95%.

Table 1. Yields and de-/ee-Values of Protected Deoxysugars **1a-7a**.

Compound	Structure[a]	Yield[b] (%)	de[c] (%)	ee[c] (%)	$[\alpha]_D^{23}$
1a		59	89	≥98	-154.7 (neat)
2a		61	87	≥98	-174.4 (c=0.91, $CHCl_3$)
3a		38	98	≥98	-197.94 (c=0.97, $CHCl_3$)
4a		43	81	≥98	-
5a		62	98	≥98	-193.85 (neat)
6a		51	98	≥98	-253.30 (c=1.02, $CHCl_3$)
7a		30	91	≥98	-192.91 (neat)

[a] As first electrophile MeI, isopropylideneglycertosylate or -iodide and second electrophile chloromethylbenzyl ether, isopropylideneglycer- and epoxypropyltosylate or -iodide were used. [b] Over all yield starting from hydrazone **9**.[c] Determined by ^{13}C-NMR spectroscopy.

In a typical procedure, a solution of 10 mmol of the hyrazone[9]**9** in 40 ml THF is deprotonated for 1.5 h at -78°C with 1.1 equiv. *t*-BuLi and than alkylated with 1.1 equiv. of e.g. methyl iodide for 1h at -95°C. After aqueous work up, the monoalkylated hydrazone is treated in the same manner with for instance chloromethylbenzyl-ether to obtain the hydrazone **10** after aqueous work up. The crude product can be cleaved directly to the desired deoxysugar by ozonolysis and purified by flash chromatography as is depicted in Scheme

1 for compound **5a**. A further reduction e.g. of compound **5a** with 1.2 equiv. L-Selectride® in 5 ml toluene at -78°C affords the corresponding diastereo- and enantiomerically pure alcohol **13** in 68% as shown in Scheme 2. Protected compounds such as **5a** can easily be deprotected *via* compound **11** using a standard hydrogenation[11] followed by an HCl-catalyzed hydrolysis[12]. The transformation can also be effected by reversing this sequence *via* compound **12**. The desired deoxysugar **5** can be isolated almost quantitatively and without any observable epimerisation after flash-cromatography. As shown in Scheme 2 polyols such as **16** can be generated from **13** in the same manner *via* the semi-protected compounds **14** or **15**.

As we recently demonstrated[13], compounds of type **6** or **7** can easily be transformed to azasugars, whose nucleoside derivatives are also potential anti-inflammatory and antitumor agents[6,7]. Furthermore, the absolute configurations of all stereogenic centers can be selected by choosing the right auxiliary (SAMP, RAMP) or electrophile. Thus, using 1,3-dioxan-5-one (**8**) in combination with the SAMP-/RAMP-hydrazone method, an efficient and highly flexible method for the diastereo- and enantioselective synthesis of natural and unnatural deoxysugars and polyols in various protected forms is now available.

Acknowledgement. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie. We thank Degussa AG, BASF AG, Bayer AG and Hoechst AG for the donation of chemicals.

References

1. Sharon, N. *Spektrum Wiss.* **1981**, 70. Brimacombe, J. S. *Angew. Chem.* **1971**, *83*, 261; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 236. Grisebach, H; Schmid, R. *Angew. Chem.* **1972**, *84*, 192; *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 159. Yoshimura, J. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 69.
2. Schmidt, R. R. *Angew. Chem.* **1986**, *98*, 213; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212. Tietze, L. F. *Nachr. Chem. Tech. Lab.* **1988**, *36*, 728.
3. Nagaoka, H.; Kishi. Y. *Tetrahedron* **1981**, *37*, 3873. Hanessian, S.; Pougny, J. R.; Boessenkool, I. K. *J. Am. Chem. Soc.* **1982**, *104*, 6164.
4. Nicolaou, K. C.; Daines, R. A.; Chakraborty, T. K.; Ogawa, Y. *J. Am. Chem. Soc.* **1988**,*110*, 4696.
5. Armstrong, R. W.; Beau, J. M.; Cheon, S. H.; Christ, W. J.; Fujioka, H; Ham, W. H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. *J. Am. Chem. Soc.* **1989**, *111*, 7225, 7530.
6. Ichikawa, Y.; Lin, Y. C.; Dumas, D. P.; Shen, G. J.; Garcia-Junceda, E.; Williams, M. A.; Bayer, R.; Ketcham, C.; Walker, L. E.; Paulson, J. C.; Wong, C. H. *J. Am. Chem. Soc.* **1992**, *114*, 9283.
7. Borman, S. *Chem. and Eng. News* **1992**, Dec. 7, 25.
8. For *de novo*-synthesis of deoxysugars see also: Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A.; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245. Roush, W. R.; Straub, J. A.; VanNieuwenhze, M. S. *J. Org. Chem. Soc.* **1991**, *56*, 1636. Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem.* **1987**, *99*, 15; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 15. Montgomery, S. H.; Pirruny, M. C.; Heathcock, C. H. *Carbohydr. Res.* **1990**, *202*, 13.
9. Enders, D.; Gatzweiler, W.; Jegelka, U. *Synthesis* **1991**, 1137. Enders, D. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: Orlando, 1984; Vol. 3, p.275. Enders, D.; Fey, P.; Kipphardt, H. *Org. Synth.* **1987**, *65*, 173, 183.
10. Enders, D.; Bockstiegel, B. *Synthesis* **1989**, 493.
11. Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746.
12. Paulsen, H; Sangster, I.; Heyns, K. *Chem Ber.* **1967**, *100*, 802.
13. Enders, D.; Jegelka, U. *Synlett* **1992**, 999.

(Received in Germany 19 January 1993)