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Organocatalytic, Biomimetic de novo Carbohydrate Synthesis and its Application to Natural Product Synthesis

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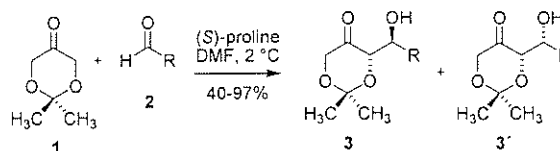
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The chemistry of carbohydrates is of enormous importance and has been investigated quite intensively.¹ Carbohydrates play key roles in many biological processes, for instance, as part of peptide- and proteoglycane, glycoproteins, nucleic acid, liposaccharids or glycolipids.² They are enantiopure building blocks (chiron approach),³ chiral auxiliaries⁴ and target molecules in general and can be adopted as biological devices or even as pharmaceuticals. Hence, chemical synthesis of carbohydrates is of great importance, even though many approaches are known.⁵ Frequently, several steps as well as protecting group manipulations are required, limiting broad application of these methods.

Nature employs dihydroxyacetonephosphate (DHAP) as a C₃-building block for carbohydrate synthesis via enzyme catalyzed aldol reactions.⁶ Accordingly, many groups focused on broadening the scope of that enzyme catalyzed reaction or the use of DHAP derivatives for chemical synthesis.⁷

Inspired by nature and the exciting reports on asymmetric organocatalysis since 2000,⁸ we have developed a simple biomimetic entry into different types of carbohydrates employing 2,2-dimethyl-1,3-dioxan-5-one (**1**, "dioxanone") as a DHAP equivalent and methylene component and different aldehydes (**2**) via an asymmetric, organocatalytic aldol reaction (Scheme 1).⁹



Scheme 1

3	R	Yield[%] ^b	anti:syn [%] ^c	ee [%] ^d
a	CH(CH ₃) ₂	97	>98:2	94
b	c-C ₆ H ₁₁	86	>98:2	90
c	C(CH ₃) ₃	-	-	-
d	CH=CHCH ₃	-	-	-
e	H	-	-	-
f	C ₆ H ₅	57	1.5:1	76 (49)
g	oCl-C ₆ H ₄	73	4:1	86 (75)
h		61	4:1	25 (5)
i		88 (93) ^e	>98:2 (>98:2) ^e	68 (84) ^e
j	CH ₂ OBn	40	>98:2	97
k	(CH ₂) ₁₃ CH ₃	62	>98:2	95
l	CH(OCH ₃)	69	94:6	90
m ^f		76	>98:2	≥98 ^g
n		80	>98:2	≥96 ^h
o ^f		31	>98:2	≥96 ^h
p		80	>98:2	≥96 ⁱ
q ^f		69	>98:2	≥96 ⁱ
r		37	>98:2	≥96 ⁱ

a General reaction conditions: 1 eq. **1**, 1 eq. **2**, 30 mol% (S)-proline, DMF, 2 °C, 3-6 d. b Yields of isolated **3** after flash-chromatography on silica gel. c Determined by ¹H- und ¹³C-NMR spectroscopy. d Determined by HPLC on chiral stationary phases. e catalyst **10** was used. f (R)-proline was used as the catalyst. g Based on the ee-value of **2**, **n**, **p** and **q**.

Table 1

Initially, we developed a general protocol for the (S)-proline-catalyzed aldol reaction between **1** and **2**. We could show for the first time, that a broad range of aldehydes is tolerated and that the corresponding aldol products **3** are obtained in moderate to excellent

¹ a) K. C. Nicolaou, H. J. Mitchell, *Angew. Chem. Int. Ed.* **2001**, *40*, 1576. b) Carbohydrate Mimics, Y. Chapleur (Ed.), Wiley-VCH, Weinheim, **1998**.

² a) M. Sznajdman in *Bioorganic Chemistry: Carbohydrates* S. M. Hecht (Ed.), Oxford University Press, New York, **1999**, 1. b) K. M. Koeller, C.-H. Wong, *Chem. Rev.* **2000**, *100*, 4465.

³ S. Hanessian, *Total Synthesis of Natural Products: The "Chiron" Approach*, Pergamon Press: Oxford, **1983**.

⁴ H. Kunz, K. Rück, *Angew. Chem. Int. Ed.* **1993**, *32*, 336.

⁵ a) T. Ogawa, *Chem. Soc. Rev.* **1994**, *23*, 397. b) S. J. Danishefsky, M. T. Bilodeau, *Angew. Chem. Int. Ed.* **1996**, *35*, 1380. c) S. Hanessian, *Preparative Carbohydrate Chemistry*, Marcel Dekker, New York, **1997**. d) T. Hudlicky, D. A. Entwistle, K. K. Pitzer, A. J. Thorpe, *Chem. Rev.* **1996**, *96*, 1195.

⁶ C.-H. Wong, T. D. Machajewski, *Angew. Chem. Int. Ed.* **2000**, *39*, 1352.

⁷ D. Enders, M. Voith, A. Lenzen, *Angew. Chem. Int. Ed.* **2005**, *44*, 1304.

⁸ a) B. List, *Synlett* **2001**, 1675. b) B. List, *Tetrahedron* **2002**, *58*, 5573. c) B. List, *Acc. Chem. Res.* **2004**, *37*, 548. d) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580.

⁹ a) D. Enders, C. Grondal, *Angew. Chem. Int. Ed.* **2005**, *44*, 1210. b) C. Grondal, D. Enders, *Tetrahedron* **2006**, *62*, 329.

yields and in most cases with good to excellent diastereo- and enantioselectivities (Table 1). Only in the case of aromatic aldehydes the yields and selectivities deteriorated, with certain examples drastically. Furthermore we could demonstrate that sterically demanding and α,β -unsaturated aldehydes are not suitable substrates. The organocatalytically accessible aldol products **3** partly represent selectively protected carbohydrates and aminosugars (Figure 1).

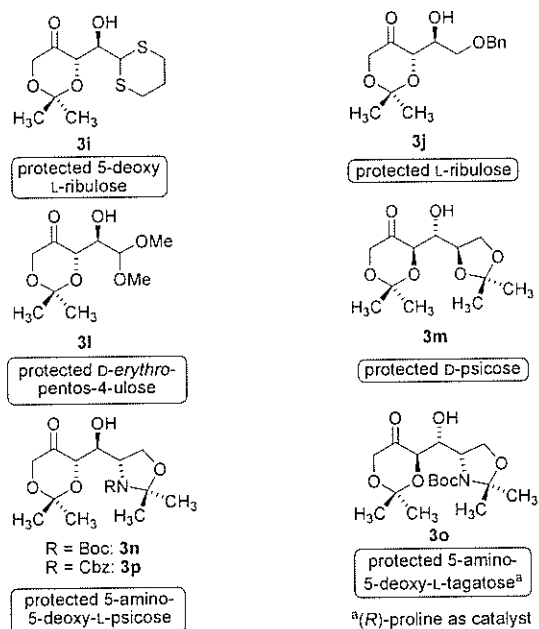
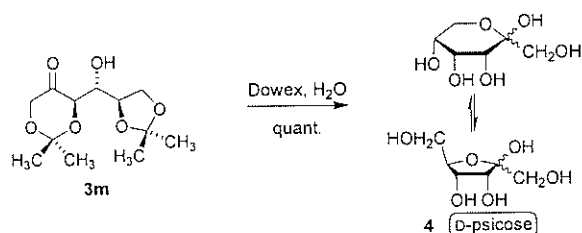


Figure 1

The deprotection could be easily carried out under acidic conditions using DOWEX ion exchange resin to afford e.g. quantitatively D-psicose (**4**) (Scheme 2).



Scheme 2

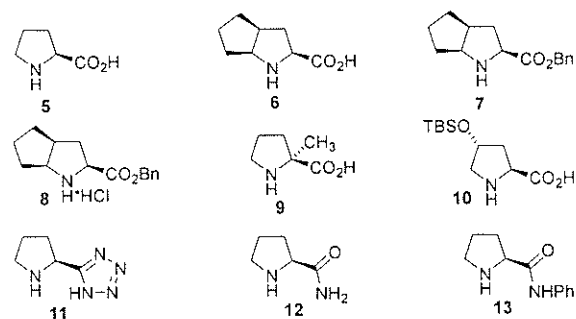
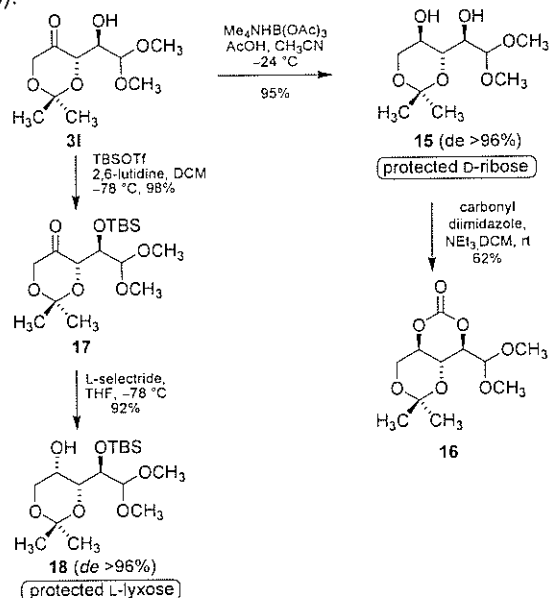


Figure 2

Besides (S)-proline, we also synthesized and employed different proline-based catalysts, but in most cases (S)-proline provides the best results. Our aim was, however, using solely proline catalysis, due to its commercial availability in both enantiomeric forms (Figure 2).

The reduction of the keto function of **3i** paves the way for a direct entry to selectively protected aldopentoses. This strategy was first described by Whitesides et al. and is known as "inversion strategy".¹⁰ We were able to accomplish both the *anti*- and the *syn*-selective reduction of **3i** to obtain protected D-ribose and protected L-lyxose (Scheme 3).

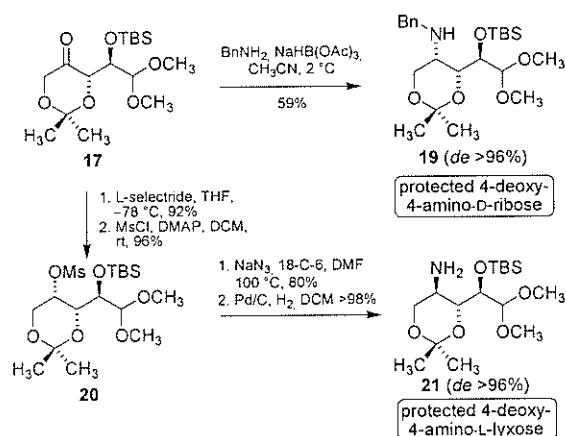


Scheme 3

Besides reduction of the keto function of **3i**, for instance reductive amination, 1,2-addition, olefination/reduction or epoxidation, deoxygenation, substitution, etc. will greatly expand the scope of this strategy and will afford different (un-)natural carbohydrates in only few steps.

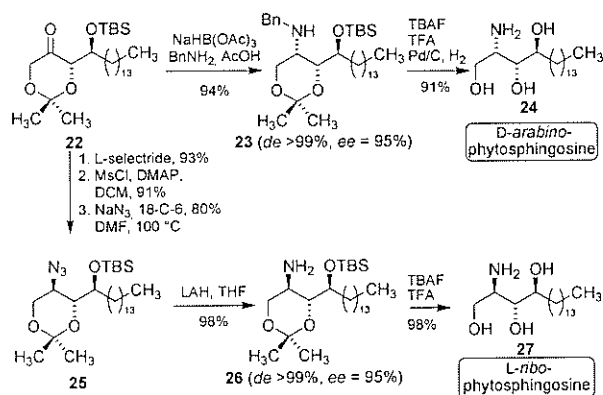
Excited by this simple entry to numerous and complex carbohydrates, we embarked with further manipulations of the keto function. First of all, we investigated the possibility of a diastereoselective reductive amination reaction. Direct reductive amination of the TBS-ether **17** with BnNH₂, NaHB(OAc)₃ and AcOH affords highly selectively the protected *anti*-1,3-aminoalcohol **19**. The stereoselective synthesis of the *syn*-1,3-aminoalcohol **21** could be achieved by mesylation of **18** to **20**, substitution with NaN₃ and subsequent reduction with Pd/C and H₂ (Scheme 4).

¹⁰ C. W. Borysenko, A. Spaltenstein, J. A. Straub, G. M. Whitesides *J. Am. Chem. Soc.* **1989**, *111*, 9275.



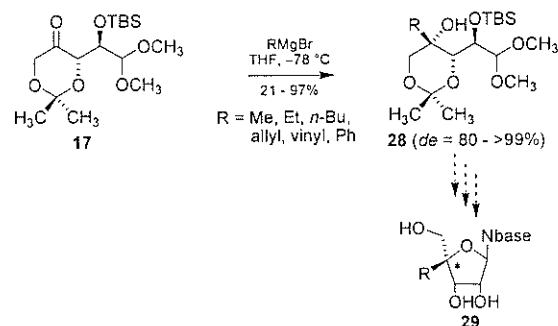
Scheme 4

Upon completion of the investigations towards the stereoselective reductive amination, we applied this concept for a direct approach to various phytosphingosines (Scheme 5).¹¹ Phytosphingosines contain very interesting and promising biological activities.¹²



Scheme 5

We have also concerned with the corresponding 1,2-addition reaction.



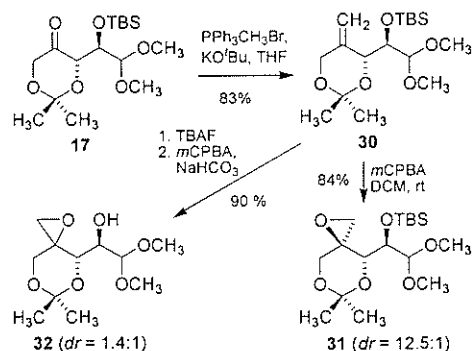
Scheme 6

¹¹ D. Enders, J. Palecek, C. Grondal, *Chem. Commun.* 2006, 655.

¹² H.-Y. Chiu, D.-L. M. Tzou, L. N. Patkar, C.-C. Lin, *J. Org. Chem.* 2003, 68, 5788 and references cited therein.

The nucleophilic carbonyl addition with different metalorganic reagents RM (R = Me, Et, *n*-Bu, allyl, vinyl, Ph, M = Mg, Ce) proceeds with good to high diastereomeric excesses ($de = 80 - >98\%$). These substituted aldohexoses could be used as modified RNA building blocks (Scheme 6).

The olefinated aldol products **30** could be employed for the synthesis of epoxisugars. Epoxidation of **30** with *m*CPBA affords **31** with a *dr* of 12.5:1, whereas the epoxidation of the free homo allyl alcohol to **32** proceeds with very low diastereoselectivity (Scheme 7).



Scheme 7

Furthermore, we were able to obtain a thiosugar derivative **33** via nucleophilic substitution of the mesylate **20** with NaSBn (Scheme 8).¹³



Scheme 8

Currently we are working on the hydrogenation of olefin **30** and the deoxygenation of **18** via a Barton-McCombie reaction to obtain the corresponding 4-deoxy-aldose.

Additionally, we envisage to use our biomimetic protocol for the asymmetric synthesis of saturated and unsaturated carbasugars, which also possess interesting biological activities.¹⁴ Currently we are working on the synthesis of the antibiotic D-carbagalactose (**34**) and its unsaturated derivative **35**, which is the 4-epimer of the natural occurring herbicidal (+) MK7607¹⁵ (Figure 3).

¹³ D. Enders, C. Grondal, *Chem. Eur. J.* in preparation.

¹⁴ P. Compain, O. R. Martin, *Bioorg. Med. Chem.* 2001, 9, 3077.

¹⁵ N. Yoshikawa, N. Chiba, T. Mikawa, S. Ueno, K. Harimaya, M. Iwata, *Jpn. Kokai Tokkyo Koho* 1994, JP 06,306,000.

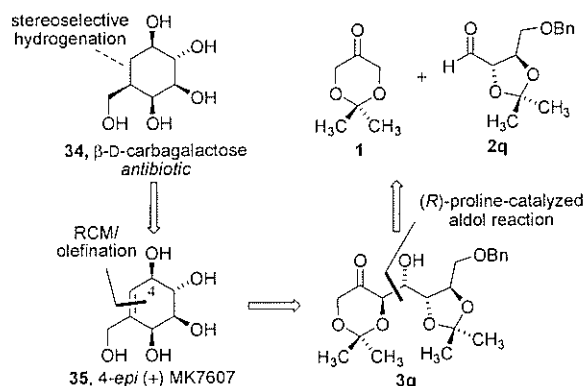
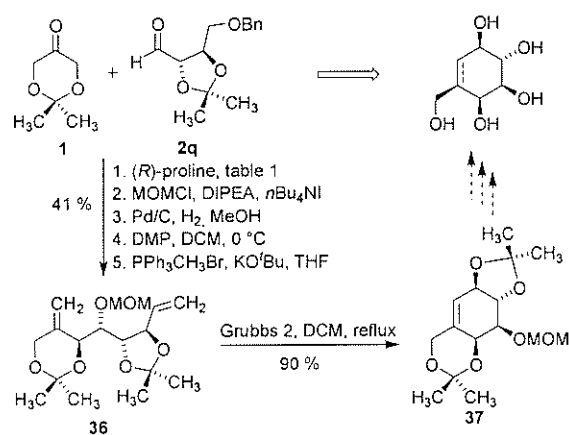


Figure 3

The (*R*)-proline-catalyzed aldol reaction between 1 and aldehyde 2q, derived from D-tartaric acid, proceeds in good yield and excellent diastereoselectivity (table 1, entry 3q). Subsequent protection with MOMCl affords the MOM-ether in 99% yield. Debzoylation, Dess-Martin-oxidation and epimerization free Wittig olefination afford RCM precursor 36 in good overall yield. The following ring closure proceeds with excellent yield (92%). In the remaining synthesis removal of the protecting groups under acidic conditions will directly afford 35, or first hydrogenation of the double bond and subsequent deprotection should deliver 34. (Scheme 9).

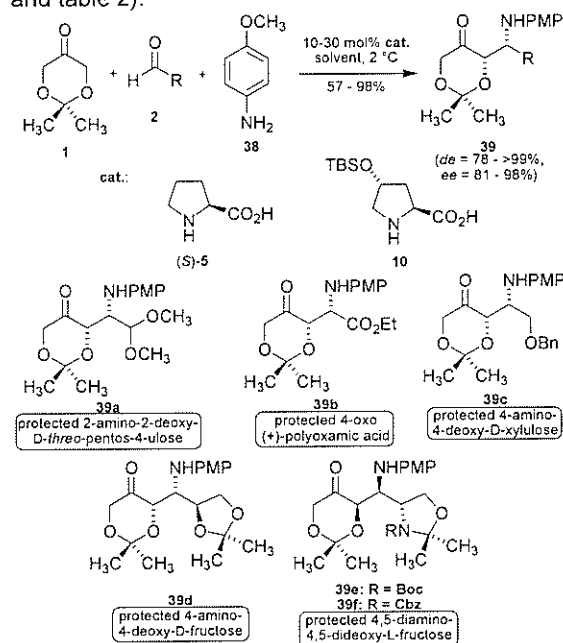


Scheme 9

During our studies towards the direct organocatalytic de novo synthesis of carbohydrates *via* proline-catalyzed aldol reaction, we considered a direct entry to aminosugars and derivatives of the latter *via* proline catalyzed three-component Mannich reaction based on our [C₃+C_x]-concept.

Thereupon we accomplished the (*S*)-proline-catalyzed reaction of dioxanone (1) with different aldehydes 2 in the presence of *p*-anisidine (38). Following comprehensive optimization of this reaction, we directly obtained various types of protected

aminosugars and derivatives of the latter (Scheme 10 and table 2).¹⁶



Scheme 10

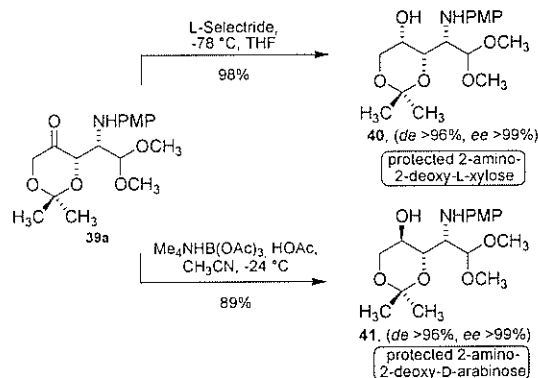
39	R	cat. [mol%]	yield [%] ^b	solvent	H ₂ O	<i>d</i> _e [%] ^c	<i>e</i> _e [%] ^d
a	CH(OCH ₃) ₂	(<i>S</i>)-5 (30)	91	DMF	4 eq.	>99 ^a	98
	CH(OCH ₃) ₂	10 (20)	98	DMF	4 eq.	>99 ^d	93
b	CO ₂ Et	(<i>S</i>)-5 (10)	91	DMF	3 eq.	≥96	98
	CO ₂ Et	10 (20)	94	DMF	-	≥96	95
c	CH ₂ OBn	(<i>S</i>)-5 (30)	94	NMP	3 eq.	60 ^d	82
	CH ₂ OBn	10 (20)	69	CH ₃ CN	5 eq.	88 ^d	96
d		(<i>S</i>)-5 (30)	57	DMF	-	80 (≥96) ^e	≥98
e		(<i>R</i>)-5 (30)	67	DMF	-	≥96	≥96 ^f
f		(<i>R</i>)-5 (30)	63	DMF	-	≥96	≥96
g		(<i>S</i>)-5 (30)	83	CH ₃ CN	-	86	≥96
		10 (20)	85	CH ₃ CN	-	≥96	≥96
h		(<i>S</i>)-5 (10)	67	NMP	-	≥96	51
		10 (20)	70	NMP	3 eq.	≥96	81
i		(<i>S</i>)-5 (30)	75	DMF	2 eq.	60 ^d	67
		10 (20)	96	DMF	5 eq.	78 ^d	87

a General reaction conditions : 2 eq. 1, 1 eq. 2, 1.1 eq. 38, 10-30 mol% cat., 2 °C, 2-5 d. b Yields of isolated 39. c Determined by NMR spectroscopy. d Determined by HPLC on chiral stationary phases. e After flash-chromatography on silica gel. f Based on the *e*_e-value of the corresponding aldehydes 2.

Table 2

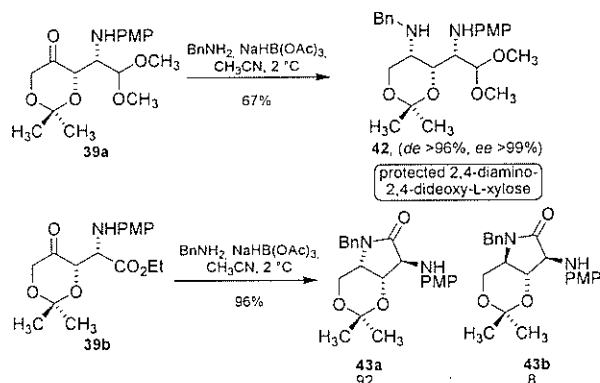
¹⁶ D. Enders, C. Grondal, M. Vrettou, G. Raabe, *Angew. Chem. Int. Ed.* 2005, 44, 4079.

The Mannich products **39** could be easily converted to the corresponding β -aminoalcohols by reduction of the ketofunction. We could demonstrate the stereoselective *syn*- and *anti*-selective reduction of **39a** to the β -aminoalcohols **40** and **41**, which both belongs to the class of biologically very important 2-amino-2-deoxysugars (Scheme 11).¹⁷



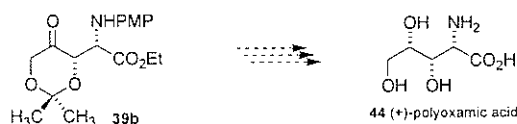
Scheme 11

Additionally, we also performed the direct reductive amination of **39a** to afford diamino-dideoxy aldopentoses. The reductive amination with BnNH₂, NaHB(OAc)₃ and AcOH generates highly *syn*-selectively the 1,3-diamine **42**. In contrast the reductive amination of **39b** leads to the formation lactams **43a** and **43b** in a 92:8 ratio (Scheme 12).¹⁸



Scheme 12

At present we are also working towards the total synthesis of (+)-polyoxamic acid (**44**) derived from **39b** (Scheme 13).



Scheme 13

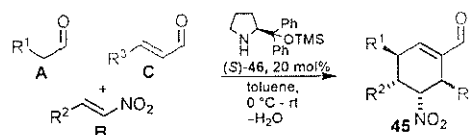
¹⁷ a) I. V. Pelyvás, C. Monneret, P. Herczegh, *Synthetic Aspects of Aminodeoxy Sugars of Antibiotics*, Springer, Berlin, 1988. b) L. Ermolenko, N. A. Sasaki, P. Potier, *J. Chem. Soc., Perkin Trans. 1*, 2000, 2465.

¹⁸ D. Enders, C. Grondal, M. Vrettou, *J. Org. Chem.* in preparation.

In summary, we have developed a highly efficient and highly diastereo- and enantioselectively organocatalytic [C₃+C_x]-concept for the direct synthesis of various carbohydrates and derivatives. The application of these building blocks enables a rapid entry to diverse carbohydrates and derived natural products (e.g. phytosphingosines, 5a-carbasugars, (+)-polyoxamic acid, etc).

Asymmetric Organocatalytic Domino Reaction.

Besides our efforts towards de novo carbohydrate synthesis we also concerned with the development of new asymmetric, organocatalytic domino reactions. These reactions bearing some advantages e.g. avoiding of time consuming purification steps and protecting group strategies, the production of waste, are environmentally friendly and they are often accompanied by excellent stereoselectivities. We have developed a triple cascade reactions with three consecutive C-C bond formations and the generation of four new stereogenic centres. This domino reaction is a Michael/Micheal/aldol condensation process with simple and readily available starting materials and we obtain diastereo- and enantioselectively *tetra*-substituted cyclohexene carbaldehydes (**45**) (Scheme 14).¹⁹



Scheme 14

We could demonstrate that all three R-groups can be varied, whereby this concept is viable for automated synthesis (table 3).

45	R ¹	R ²	R ³	Yield [%] ^a	<i>d</i> ^b	<i>de, ee</i> [%] ^c
a	Me	Ph	Ph	40 (70)	7.8:2.2	>99
b	Me	<i>o</i> CIPh	Ph	51 (61)	8.4:1.6	>99
c	Me	<i>p</i> MeOPh	Ph	38 (65)	8.3:1.7	>99
d	Me	Piperonyl	Ph	39 (64)	8.7:1.3	>99
e	Et	Ph	Ph	58 (60)	8.0:2.0	>99
f	<i>i</i> -Pr	Ph	Ph	56 (62)	7.9:2.1	>99
g	Bn	Ph	Ph	38 (45)	8.9:1.1	>99
h	Me	Ph	Me	25 (32)	6.8:3.2	>99
i	Me	Ph	<i>n</i> Bu	29 (33)	8.0:2.0	>99

^a Yield of the isolated main diastereomer (in parenthesis: yield of the crude main diastereomer determined by GC).

^b The diastereomeric ratio (*d.r.*) was determined by GCMS.

^c The diastereo- and enantiomeric excess (*de, ee*) was determined by HPLC on a chiral stationary phase

Table 3

These cyclohexene carbaldehydes can now used as flexible building blocks in organic synthesis, what is currently investigated in our laboratories.

¹⁹ D. Enders, M. R. M. Hüttli, C. Grondal, G. Raabe, *Nature* submitted.