Chiral Piperidine Derivatives

Stereoselective Solid-Phase Synthesis of Chiral Piperidine Derivatives by Using an Immobilized Galactose Auxiliary**

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Drug development[1] has significantly been accelerated by exploiting combinatorial solid-phase synthetic methodologies.[2] Although enantiomerically pure compounds[3] are of major interest for the pharmaceutical industry only few stereoselective syntheses on the solid-phase have been reported so far. Besides polymer-bound chiral ligands and catalysts[4] some immobilized chiral auxiliaries and their application in aldol condensations,[5] conjugate additions,[6] 1,3-dipolar cycloadditions,[7] or radical allylations[8] have been described.

Recently, we reported on the synthesis of an immobilized galactosylamine as auxiliary and its employment in stereoselective Ugi reactions on the solid-phase.[9] Within this approach a galactosyl azide as precursor was coupled to hydroxyfunctionalized polymers, for example Wang resin, through the sterically demanding α,α,α′,α′-tetramethyl azelaic acid and subsequently reduced to the galactosylamine on the solid-phase. Major disadvantages of this anchoring for application in other solid-phase reactions lay in the acid lability of the Wang anchor and in the low loading of the polymer with the galactosylamine.

Herein, we report diastereoselective domino Mannich–Michael condensations[10] performed with an immobilized glycosylamine as the auxiliary, allowing reactions with Lewis acids and organometallic reagents. Thus, a polymer-bound chlorodiisopropylsilane[11,12] was attached to the carbohydrate auxiliary through a hydroxyfunctionalized spacer unit, which enabled facile cleavage of reaction products from the solid-phase by mild fluoridolysis.[13] Linkages of substrates through sterically demanding silyl ethers have proven stable towards a variety of organometallic reagents. Similar strategies have been applied for the synthesis of oligosaccharides,[14] polyketides,[15] and prostaglandins.[16]

For the assembly of the galactose auxiliary 1,6-hexanediol was monosilylated with *tert*-butyldiphenylsilyl chloride, the remaining hydroxy function was transformed to bromide to give **1** under Appel conditions. Compound **1** was then allowed to react with isobutyric acid dianion to give α,α-branched octanoic acid **2** (Scheme 1). The acid chloride obtained from **2** was regioselectively esterified with the primary hydroxy function of galactosyl azide **3**. After pivaloylation[17] of the

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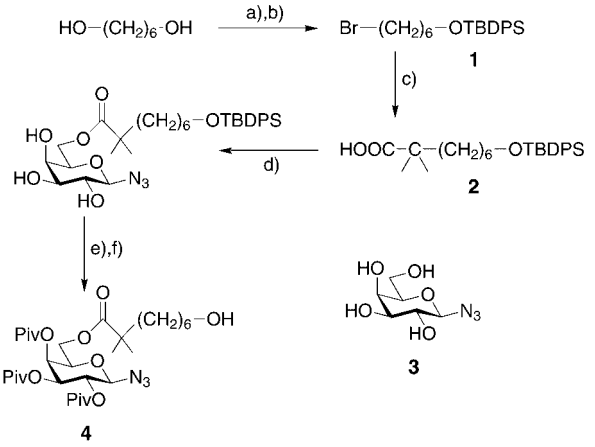
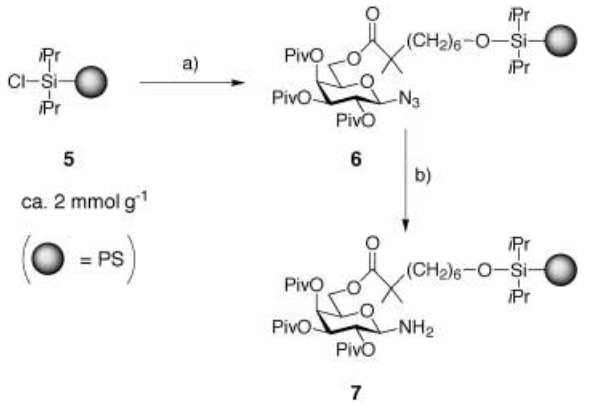


Scheme 1. Solution synthesis of **4**. a) TBDPSCl, imidazole, DMF, 20 °C, 88 %; b) CBr_4, PPh_3, CH_2Cl_2, 0 °C→20 °C, 85 %; c) $Me_2C{=}C(OLi)_2$, THF, −20→40 °C, 77 %; d) 1. $C_2O_2Cl_2$, CH_2Cl_2, 20 °C, 2. β-D-galactopyranosyl azide (**3**), pyridine, DMAP, 60 °C, 49 %; e) PivCl, pyridine, 60 °C, 85 %; f) TBAF·3 H_2O, THF, 20 °C, 85 %. TBDPS = *tert*-butyldiphenylsilyl, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, Piv = pivaloyl (*t*BuCO), TBAF = tetra-*n*-butylammonium fluoride, DMF = dimethylformamide.

remaining hydroxy groups and removal of the silyl protecting groups, galactosyl azide **4** was coupled to the polymer-bound chlorosilane **5** through a hexamethylene spacer (Scheme 2). Owing to the high loading (ca. 2 mmol g^{-1}) of **5** (see ref. [11] for synthesis) almost complete coupling was observed when 0.25 equivalents of galactosyl azide **4** were subjected to etherification. Methanolysis of the unreacted chlorosilane groups furnished polymer-bound galactosyl azide **6** with a loading of about 0.38 mmol g^{-1}, which corresponds to an average substitution of every tenth styrene unit with the carbohydrate moiety (Scheme 2).[18] Reduction of the galactosyl azide with ten equivalents each of 1,3-propanedithiol and triethylamine in DMF gave immobilized galactosylamine **7** quantitatively and without anomerization. Both the coupling with the glycosyl azide ($\tilde{\nu}_{C=O} = 1742\ cm^{-1}$, $\tilde{\nu}_{azide} = 2116\ cm^{-1}$) and the azide reduction were monitored by IR spectroscopy.

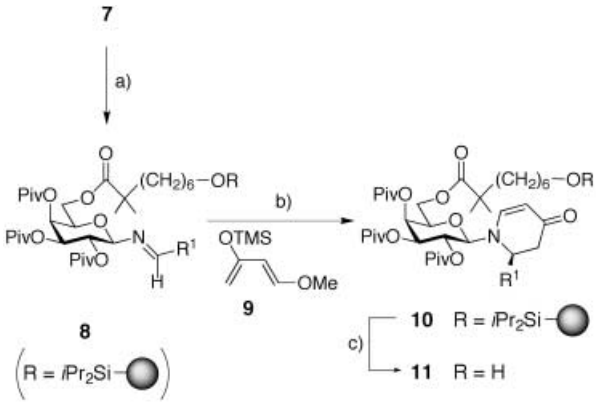


Scheme 2. Synthesis of the immobilized galactosylamine. a) 1. imidazole, **4** (0.25 equiv), CH_2Cl_2, 20 °C, 12 h, 2. addition of MeOH, 24 h; b) 1,3-propanedithiol, NEt_3 (each 10 equiv), DMF, 20 °C, 12 h. PS = polystyrene.

To optimize reaction and cleavage conditions with this system we initially performed model Ugi reactions using the galactosylamine **7**. Fluoridolysis with tetra-*n*-butylammonium fluoride (TBAF) gave the corresponding Ugi condensation products in high yields and in diastereomeric ratios (80–92 % *de*) comparable to those obtained for analogous syntheses in solution[19] and on the solid-phase.[9]

Encouraged by these results we employed galactosylamine **7** for the stereoselective synthesis of heterocycles. The domino Mannich–Michael condensation of glycosyl imines with the electron-rich Danishefsky's diene opens up a stereoselective access to 2-substituted *N*-galactosyl-5,6-dehydropiperidin-4-ones,[10] which are valuable synthons for the synthesis of nitrogen heterocycles.[20]

So far, only three combinatorial syntheses of didehydropiperidin-4-ones have been reported, all of them based on different methodologies, but all giving racemic products.[21] Herein we describe the first stereoselective synthesis of chiral dehydropiperidinones on the solid-phase. The immobilized galactosylamine auxiliary **7** was transformed to the corresponding galactosyl imines **8** with high *E*-isomeric and β-anomeric purity by acid-catalyzed condensation (Scheme 3).



Scheme 3. Solid-phase synthesis of didehydropiperidinones. a) R^1CHO (5 equiv), AcOH (10 equiv), toluene, 20 °C, 6 h; b) Danishefsky's diene **9** (10 equiv), $ZnCl_2$ (5 equiv), THF, 20 °C, 48 h; c) TBAF·3 H_2O (5 equiv based on silyl units), AcOH (1.7 equiv), THF, 20 °C, 48 h.

It is noteworthy that analogous conditions applied to the solution process led to an irreversible anomerization giving the thermodynamically more stable and less reactive α-imines. According to IR spectroscopy trimethyl orthoformate[22] was found to be an unsuitable dehydrating agent. Subsequent domino Mannich–Michael condensation at room temperature with Danishefsky's diene **9** gave resin-bound didehydropiperidinones **10**, which could be cleaved from the polymeric support with TBAF (1 M solution in THF, buffered with AcOH). The LC-MS analysis of the resulting crude products **11**[23] showed that they were formed in high purity, yield, and diastereoselectivity (Table 1), despite the relatively high temperature (22 °C). The diastereomeric excesses of the 2-alkyl didehydropiperidinones **11l–o** and **11q** were found to be lower than those of the 2-aryl analogues. Only a slight increase of the diastereomeric ratio was observed when the reaction was performed at lower temperature.

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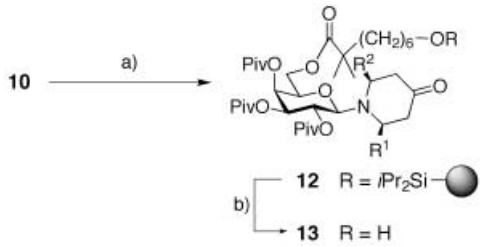
Table 1: Diastereoselective synthesis of didehydropiperidinones on the solid-phase according to Scheme 3.

Compound	R	Yield [%][a]	Purity [%][b]	d.r.[b]
11a	C_6H_5	77	98	97:3
11b	*p*-Cl-C_6H_4	77	92	97:3
11c	*p*-O_2N-C_6H_4	40	80	94:6
11d	*p*-F-C_6H_4	73	97	98:2
11e	*m*-F-C_6H_4	n.d.	91	100:0
11f	*p*-NC-C_6H_4	75	93	99:1
11g	*p*-F_3C-C_6H_4	81	97	98:2
11h	2-Cl-6-F-C_6H_3	49	89	93:7
11i	*m*-Br-C_6H_4	57	95	99:1
11j	*p*-Br-C_6H_4	n.d.	97	96:4
11k	*p*-MeO-C_6H_4	80	98	98:2
11l	CH_2CH_2-C_6H_5	50	83	90:10
11m	*n*-C_7H_{15}	57	74	89:11
11n	*n*-C_5H_{11}	76	95	87:13
11o	CH_2-$CH(CH_3)_2$	61	88	84:16
11p	$CH(CH_3)_2$	70	92	98:2
11q	CH_3	73	90	80:20

[a] Yield of crude product (four steps); based on initial loading of **6**. [b] Determined by LC-MS (evaporative light scattering (ELS) /UV detection). n.d. not determined.

For further functionalization resin-bound enaminones **10** were subjected to conjugate addition reactions. The reaction with L-selectride as hydride donor under different reaction conditions only gave mixtures of 1,2- and 1,4-reduced products. The reduction in the presence of the oxygenophilic Lewis acid methylaluminum bis[2,6-di-*tert*-butyl-4-methylphenoxide] (MAD),[24] however, after cleavage from resins **12a–e** yielded the chemoselectively 1,4-reduced piperidinones **13a–e** (Scheme 4, Table 2). As shown for the release of



Scheme 4. Conjugate hydride and cuprate addition to polymer-bound enones **10**. a) For R^2 = H: L-Selectride (10 equiv), MAD (20 equiv), THF/toluene, −20 °C, 4 h; for R^2 = alkyl: $(R^2)_2Cu(CN)Li_2$ (15 equiv), $BF_3{\cdot}OEt_2$ (15 equiv), THF, −60 °C→−15 °C, 14 h; b) TBAF·3 H_2O (5 equiv based on silyl units), AcOH (1.7 equiv), THF, 20 °C, 48 h.

the corresponding piperidinone from resin **12c**, cleavage from the polymer-bound auxiliary can be accomplished by treatment with dilute trifluoroacetic acid in the presence of dimethyl sulfide and water giving rise to the corresponding piperidine trifluoroacetate. In this case, the piperidine derivative was isolated in 53% yield. The conditions chosen are so mild that the acid-sensitive anchoring of the auxiliary to the solid-phase is not affected all. Piperidinones can be released from *N*-galactosyl derivatives **13** according to the previously reported methodology.[10]

Table 2: Conjugate hydride and cuprate addition to polymer-bound enones according to Scheme 4.

Compound	R^1	R^2	Yield [%][a]	Purity [%][b]	*cis*/*trans*[b]
13a	*p*-Cl-C_6H_4	H	34	65	–
13b	*m*-F-C_6H_4	H	53	95	–
13c	*p*-F_3C-C_6H_4	H	n.d.	83	–
13d	*p*-Br-C_6H_4	H	38	82	–
13e	$CH(CH_3)_2$	H	60	70	–
13f	*m*-F-C_6H_4	*n*Bu	75	49	98:2
13g	*p*-F_3C-C_6H_4	*n*Bu	76	61	93:7
13h	*m*-Br-C_6H_4	*n*Bu	71	78	95:5
13i	2-Cl-6-F-C_6H_3	Me	67	78	96:4

[a] Yield of crude product (five steps); based on initial loading of **6**. [b] Determined by LC-MS (ELS/UV detection). n.d. not determined.

As 2,6-disubstituted piperidines are a widespread structural motif in natural products we are also interested in a stereoselective solid-phase approach to this class of compounds. Among many cuprate reagents tested cyano-modified Gilman reagents (Lipshutz cuprates)[25] in the presence of $BF_3{\cdot}OEt_2$ were found to be the reagents of choice for the conjugate cuprate addition to polymer-bound enones **10**. Cleavage from the polymeric support gave *N*-galactosylated 2,6-disubstituted piperidinones **13f–i** in high yields and excellent *cis* selectivity (Scheme 4, Table 2).

The fluoride-labile anchoring strategy of the galactosylamine as immobilized auxiliary described herein and its application in domino Mannich–Michael condensations leads to almost diastereomerically pure products even at room temperature. The products are obtained in high purity without the necessity for tedious separation procedures. The dehydropiperidinones formed stereoselectively on the solid-phase can be subjected to further functionalization as was shown by conjugate addition reactions. Consequently, the methodology presented herein enables rapid combinatorial access to structurally diverse chiral piperidine derivatives.

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[1] a) R. G. Franzén, *J. Comb. Chem.* **2000**, *2*, 195–214; b) R. E. Dolle, *J. Comb. Chem.* **2001**, *3*, 477–517; c) R. E. Dolle, *J. Comb. Chem.* **2002**, *4*, 369–418; d) B. Lou, *Drug Discovery Today* **2001**, *6*, 1288–1294; e) A. Ganesan, *Drug Discovery Today* **2002**, *7*, 47–55.

[2] a) *Combinatorial Chemistry—Synthesis, Analysis, Screening* (Ed.: G. Jung), Wiley-VCH, Weinheim, **1999**; b) *Solid-Phase Organic Synthesis* (Ed.: K. Burgess), Wiley, New York, **1999**; c) F. Zaragoza Dörwald, *Organic Synthesis on Solid Phase*, Wiley-VCH, Weinheim, **2000**; d) P. Seneci, *Solid-Phase Synthesis and Combinatorial Technologies*, Wiley, New York, **2000**; e) *Solid-Phase Organic Syntheses, Vol. 1* (Ed.: A. W. Czarnik), Wiley, New York, **2001**; f) *Handbook of Combinatorial Chemistry* (Eds.: K. C. Nicolaou, R. Hanko, W. Hartwig), Wiley-VCH, Weinheim, **2002**.

[3] a) S. C. Stinson, *Chem. Eng. News* **2001**, *79*(20), 45–56; b) A. M. Rouhi, *Chem. Eng. News* **2002**, *80*(23), 43–50.

[4] Reviews: a) S. J. Shuttleworth, S. M. Allin, R. D. Wilson, D. Nasturica, *Synthesis* **2000**, 1035–1074; b) Y. R. de Miguel, *J. Chem. Soc. Perkin Trans. 1* **2000**, 4213–4221.

  1433-7851/03/4207-0789 $ 20.00+.50/0

[5] A. V. Purandare, S. Natarajan, *Tetrahedron Lett.* **1997**, *38*, 8777 – 8780.
[6] C. W. Phoon, C. Abell, *Tetrahedron Lett.* **1998**, *39*, 2655 – 2658.
[7] G. Faita, A. Paio, P. Quadrelli, F. Rancati, P. Seneci, *Tetrahedron Lett.* **2000**, *41*, 1265 – 1269.
[8] E. J. Enholm, M. E. Gallagher, S. Jiang, W. A. Batson, *Org. Lett.* **2000**, *2*, 3355 – 3357.
[9] K. Oertel, G. Zech, H. Kunz, *Angew. Chem.* **2000**, *112*, 1489 – 1491; *Angew. Chem. Int. Ed.* **2000**, *39*, 1431 – 1433.
[10] a) H. Kunz, W. Pfrengle, *Angew. Chem.* **1989**, *101*, 1041 – 1042; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 1067 – 1068; b) M. Weymann, W. Pfrengle, D. Schollmeyer, H. Kunz, *Synthesis* **1997**, 1151 – 1160.
[11] The polymer-bound chlorosilane is easily prepared with a loading capacity of about 2 mmol g^{-1} by direct lithiation of commercially available polystyrene resin (crosslinked with 1% divinylbenzene, 100–200 mesh) with *n*BuLi and subsequent treatment with dichlorodiisopropylsilane (see also ref. [12]).
[12] M. J. Farrall, J. M. J. Fréchet, *J. Org. Chem.* **1976**, *41*, 3877 – 3882.
[13] This enables the direct analysis of diastereomeric *N*-galactosylated products and of potential side products and facilitates the analysis of complex reaction sequences on the solid-phase.
[14] a) S. J. Danishefsky, K. F. McClure, J. T. Randolph, R. B. Ruggeri, *Science* **1993**, *260*, 1307 – 1309; b) J. T. Randolph, K. F. McClure, S. J. Danishefsky, *J. Am. Chem. Soc.* **1995**, *117*, 5712 – 5719.
[15] a) C. Gennari, S. Ceccarelli, U. Piarulli, K. Aboutayab, M. Donghi, I. Paterson, *Tetrahedron* **1998**, *54*, 14999 – 15016; b) I. Paterson, M. Donghi, K. Gerlach *Angew. Chem.* **2000**, *112*, 3453 – 3457; *Angew. Chem. Int. Ed.* **2000**, *39*, 3315 – 3319.
[16] a) L. A. Thompson, F. L. Moore, Y.-C. Moon, J. A. Ellman, *J. Org. Chem.* **1998**, *63*, 2066 – 2067; b) D. R. Dragoli, L. A. Thompson, J. O'Brien, J. A. Ellman, *J. Comb. Chem.* **1999**, *1*, 534 – 539.
[17] The presence of the pivaloyl group at C-2 is necessary for effective diastereofacial differentiation of glycosyl imines (review: K. Rück, H. Kunz, *Angew. Chem.* **1993**, *105*, 355 – 377; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 336 – 358); the other hydroxy functions are pivaloyl or pseudopivaloyl (as at C-6 in **4**) protected, to increase the stability of the auxiliary against organometallic reagents.
[18] The loading capacity was calculated from the nitrogen content of a resin sample that was washed thoroughly and dried for 48 h at 40 °C under high vacuum.
[19] H. Kunz, W. Pfrengle, *J. Am. Chem. Soc.* **1988**, *110*, 651 – 652.
[20] H. Kunz, M. Weymann, M. Follmann, P. Allef, K. Oertel, M. Schultz-Kukula, A. Hofmeister, *Pol. J. Chem.* **1999**, *73*, 15 – 27. *N*-Carbamoyl-5,6-didehydropiperidin-4-ones and their functionalization have been studied extensively by Comins et al.: D. L. Comins, *J. Heterocycl. Chem.* **1999**, *36*, 1491 – 1500.
[21] a) Y. Wang, S. R. Wilson, *Tetrahedron Lett.* **1997**, *38*, 4021 – 4024; b) M. W. Creswell, G. L. Bolton, J. C. Hodges, M. Meppen, *Tetrahedron* **1998**, *54*, 3983 – 3998; c) B. Munoz, C. Chen, I. A. McDonald, *Biotechnol. Bioeng.* **2000**, *71*, 78 – 84.
[22] G. C. Look, M. M. Murphy, D. A. Campbell, M. A. Gallop, *Tetrahedron Lett.* **1995**, *36*, 2937 – 2940.
[23] After evaporation of the combined cleavage and washing solutions, the residue was subjected to filtration through a short plug of silica, the crude product was eluted with petroleum ether/ethyl acetate (1/1), and after removal of the solvent the residue was analyzed by HPLC-MS.
[24] K. Maruoka, K. Nonoshita, H. Yamamoto, *Tetrahedron Lett.* **1987**, *28*, 5723 – 5726.
[25] B. H. Lipshutz, R. S. Wilhelm, D. M. Floyd, *J. Am. Chem. Soc.* **1981**, *103*, 7672 – 7674.

  1433-7851/03/4207-0790 $ 20.00+.50/0