Pergamon

Tetrahedron Letters 40 (1999) 7783–7786

TETRAHEDRON LETTERS

Combinatorial Solid-Phase Synthesis Using D-Galactose as a Chiral Five-Dimension-Diversity Scaffold

Christopher Kallus,[a] Till Opatz,[a] Tobias Wunberg,[a] Wolfgang Schmidt,[b] Stefan Henke,[b] and Horst Kunz[a]*
a) Institut für Organische Chemie der Universität Mainz, D-55099 Mainz, Germany;
b) Hoechst Marion Roussel Deutschland GmbH, D-65926 Frankfurt/M., Germany.

Received 26 August 1999; accepted 3 September 1999

Abstract: All five hydroxy groups of galactose as the scaffold are used for selective coupling of side chains in a combinatorial methodology by application of a set of orthogonally stable protecting groups in combination with a thioglycoside anchor.

Keywords: Combinatorial chemistry, Carbohydrates, Protecting groups, Solid-phase synthesis.

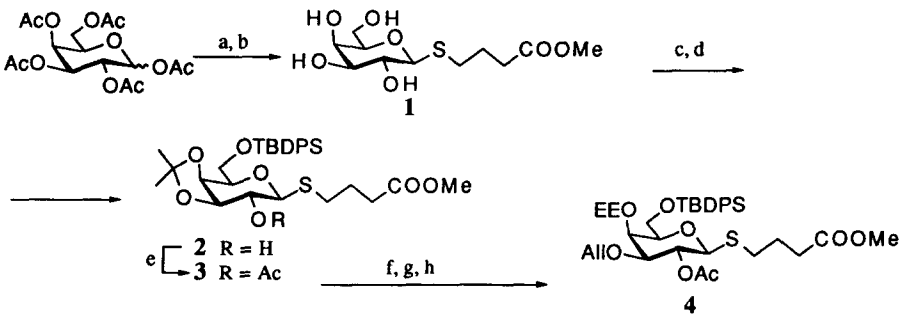
Combinatorial syntheses[1] are often carried out as sequential condensation and addition reactions on solid-phase-linked substrates. As an alternative, polyfunctional scaffolds, e. g. cholic acid derivatives[2] or squaric acid,[3] have been used in order to achieve molecular diversity. Compared to these scaffolds, carbohydrates contain more functional groups. In addition, they provide a number of stereogenic centers useful for a defined spatial presentation of substituents. Hirschmann, Nicolaou et al. utilized these properties of glucopyranose for the construction of β-turn peptidomimetics.[4] Similarly, D-glucose was converted into a mimic of hapalosin.[5] Recently, amino deoxy-glucuronic acid derivatives have been modified in three positions.[6] If monosaccharides are to be exploited as multifunctional scaffolds in combinatorial synthesis,[7] a set of four selectively removable hydroxy protecting groups must be combined with a cleavable linker. The linker has to be stable throughout all protecting group manipulations and substitution reactions. Moreover, the remaining protecting groups must be stable during the substitution reaction at every deblocked hydroxy group.

Using galactopyranose as the scaffold, we show here that all five positions of the carbohydrate, not only three[6] or four,[7] can be selectively modified in a combinatorial strategy. Scaffold **1** equipped with a carboxy-functionalized thioglycoside anchor was obtained from penta-acetyl-galactopyranose and methyl 4-mercapto-butyrate/BF_3 etherate (scheme 1) and subsequent removal of the O-acetyl groups. Reaction of **1** with tert-butyl-diphenylsilyl chloride/imidazole and introduction of the 3,4-isopropylidene group furnished galactose derivative **2** which is a candidate for solid-phase model reactions (Scheme 2).

In order to differentiate all three secondary hydroxy groups, 2-OH of **2** was acetylated. Selective acidolysis of the isopropylidene group of **3** without affecting its 6-OTBDPS ether was achieved by treatment with ethane-1,2-dithiol and cat. amounts of p-Ts-OH in refluxing $CHCl_3$. Regioselective allylation at the 3-OH via a stannylene intermediate[8] and subsequent acid-catalyzed addition of ethyl vinyl ether at 4-OH furnished scaffold **4** carrying a set of orthogonally stable protecting groups.

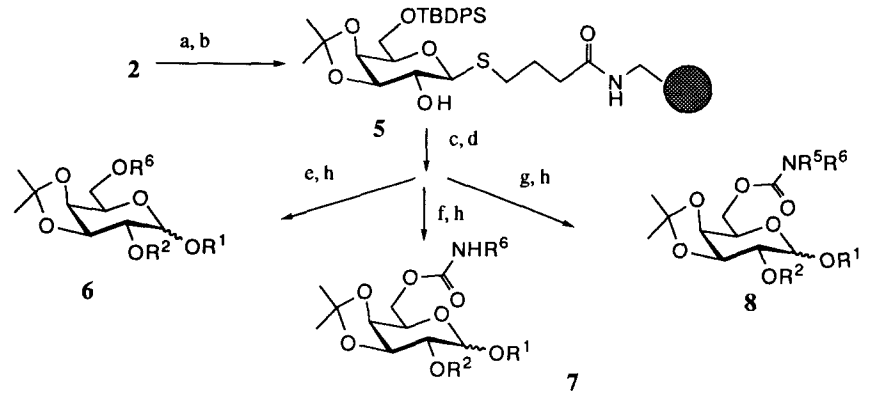
In order to examine the thioglycoside anchor in solid-phase syntheses, the methyl ester of **2** was hydrolyzed by LiOH in aq. MeOH/THF and the resulting carboxylic acid coupled to aminomethyl polystyrene (100 - 200 mesh, 1.3 mmol /g) using diisopropylcarbodiimide (DIC)/ 1-hydroxybenzotriazole (HOBt).

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01690-1



Scheme 1: a) HS-$(CH_2)_3$COOMe/BF_3·Et_2O, CH_2Cl_2; 90 %; b) NaOMe, MeOH; quant. c) $tBuPh_2SiCl$/ imidazole, DMF; 74 %; d) 2,2-dimethoxypropane, cat. p-TsOH; 90 %; e) Ac_2O/pyridine; 82 %; f) ethane-1,2-dithiol, cat. p-TsOH, $CHCl_3$, 74 %; g) Bu_2SnO, AllBr, Bu_4NI; benzene, 80°C; 63 %; h) ethyl vinyl ether, cat. p-TsOH, CH_2Cl_2, 69 %.

In first O-alkylation reactions on scaffold **5** it became evident, that the second alkylation (at O-6) proceeded incompletely. We assumed that the 6-alkoxides are locked in ion pairs with quaternary ammonium cations formed during the first alkylation reaction (at O-2) from the non-acylated amino groups of the polymer. Therefore, a capping reaction was performed after the coupling to the polymer. In order to ascertain a high amino selectivity leaving the 2-OH of **5** unaffected, **5** was reacted with acetic acid and the efficient peptide condensing reagent N,N'-bis (tetramethylene)-O-pentafluorophenyl uronium hexafluorophosphate (PfPyU).[9]

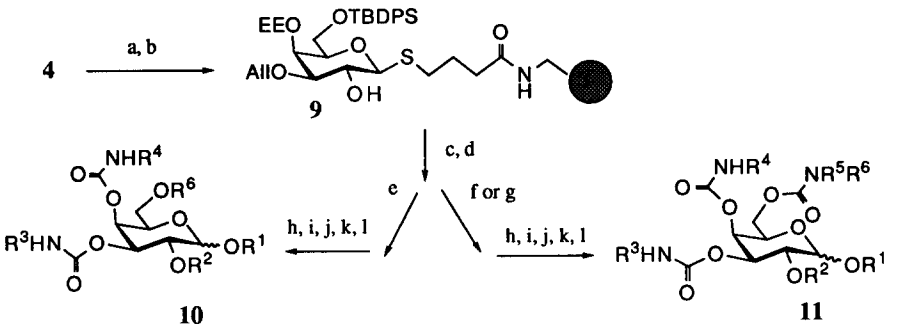


Scheme 2: a) LiOH, THF, MeOH, H_2O; 97 %; b) aminomethyl polystyrene, DIC, HOBt, capping; load 0.75 mmol/g c) KOtBu, R^2-X, 18-crown-6, DMF; d) Bu_4NF, THF; e) KOtBu, R^6-X, 18-crown-6, DMF; f) R^6NCO, 4-dimethylaminopyridine (DMAP),[10] dioxane; g) carbonyl diimidazole (CDI), KOtBu, DMAP, R^5R^6NH, DMF; h) Br_2, 2,6-di-tert.-butylpyridine, CH_2Cl_2, cyclohexene, R^1-OH, Et_4NBr.

After this pretreatment, **5** was subjected to sequences of deprotonation using KOtBu, alkylation in the presence of 18-crown-6, desilylation using tetrabutylammonium fluoride and either a second alkylation, a reaction with an isocyanate or with carbonyl diimidazole (CDI) and subsequent addition of an amine to furnish the correspending polymer-linked products. Addition of bromine/di-tert-butylpyridine (DTBP) and trapping of

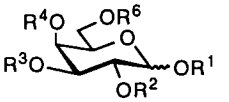
excess Br_2 by cyclohexene cleaved the thioglycoside anchor. The formed galactosyl bromide was activated by tetraethylammonium bromide[11] and reacted with alcohol R^1-OH to yield the products of type **6**, **7** or **8**, respectively (Scheme 2, Table 1).

In order to exploit all five functional dimensions of diversity, **4** was treated with LiOH/aq. MeOH/THF, coupled to aminomethyl polystyrene and subjected to the capping process.



Scheme 3: a) LiOH, THF, MeOH, H_2O; 97 %; b) aminomethyl polystyrene, DIC, HOBt, capping; load 0.75 mmol/g; c) KOtBu, R^2-X, 18-crown-6, DMF; d) Bu_4NF, THF; e) KOtBu, R^6-X, 18-crown-6, DMF; f) R^6NCO, 4-dimethylaminopyridine,[10] dioxane; g) CDI, KOtBu, DMAP, R^5R^6NH, DMF; h) cat. p-TsOH, dioxane/MeOH 10 : 1; i) R^4NCO, DMAP, dioxane; j) $[IrH_2COD(PMePh_2)_2]PF_6$, dioxane, catal. p-TsOH, dioxane/MeOH 10 :1; k) R^3NCO, DMAP, dioxane; l) Br_2, 2,6-di-tert.-butylpyridine, CH_2Cl_2, cyclohexene, R^1-OH, Et_4NBr.

Table 1 Combinatorial Synthesis of Galactose Derivatives According to Schemes 2 and 3



Product	R^1	R^2	R^3	R^4	R^6	Yield (%)[a]
6a	Me	Bn	-Isopropylidene-		Pr	42
6b	Me	Bn	-Isopropylidene-		$tBuO_2CCH_2$	29
6c	Me	Bn	-Isopropylidene-		3,5-$(CF_3)_2$-Bn	35
7a	Me	Hep	-Isopropylidene-		2-CF_3-PhNHCO	69
7b	Me	2-CN-Bn	-Isopropylidene-		2-CF_3-PhNHCO	34
7c	Me	Bn	-Isopropylidene-		2-NO_2-PhNHCO	66
8a	Me	Bn	-Isopropylidene-		Et_2NCO	79
8b	Me	Bn	-Isopropylidene-		BnNHCO	42
8c	Et	Bn	-Isopropylidene-		Et_2NCO	64
8d	*i*Pr	4-Br-Bn	-Isopropylidene-		$tBuO_2CCH_2NHCO$	52
10a	Me	Bn	4-Cl-PhNHCO	2-NO_2-PhNHCO	$tBuO_2CCH_2$	6
10b	Me	4-Br-Bn	4-Cl-PhNHCO	2-NO_2-PhNHCO	Hep	38
11a	Me	4-*t*Bu-Bn	2-NO_2-PhNHCO	4-Cl-PhNHCO	Et_2NCO	23
11b	Me	Hep	4-CN-PhNHCO	2-CF_3-PhNHCO	2-NO_2-PhNHCO	16

[a] Isolated yield after chromatography on silica gel

Polymer-linked scaffold **9** was sequentially subjected to deprotonation, alkylation at O-2, desilylation, alkylation or carbamoylation at O-6, removal of the EE-ether using cat. pyridinium p-toluene sulfonate, carbamoylation, isomerization of the 3-O-allyl ether using cat. [cyclooctadiene-bis(methyldiphenylphosphino)-hydridoiridium] hexafluorophosphate[12] and acidolysis of the propenyl ether, carbamoylation of 3-OH, cleavage of the thioglycoside anchor and glycosylation of R^1-OH after in situ anomerization of the galactosyl bromide (Scheme 3).

Products of type **10** and **11** were isolated after purifaction by chromatography predominantly as the α-anomers. They have been identified by RP-HPLC, mass spectrometry and for typical examples by NMR spectroscopy.[13]

Several hundred compounds of structures **6, 7, 8, 10** and **11** have been prepared using this strategy and are currently tested for biological activity. The high structural diversity available by using carbohydrate scaffolds can be even wider expanded when the concept is applied to other monosaccharides or disaccharides. Investigations in this direction are in progress.

References and Notes

1) Reviews: a) L. A. Thomson, J. A. Ellman, *Chem. Rev.* **1996**, *96*, 555; b) F. Balkenhohl, C. v. d. Busche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2136; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288; c) A. Netzi, J. M. Ostresh,Houghten, R. A. *Chem. Rev.* **1997**, *97*, 449; d) S. Kobayashi, *Chem. Soc. Rev.* **1999**, *28*, 1.
2) a) G. Wess, K. Bock, H. Kleine, M. Kurz, W. Guba, H. Hemmerle, E. Lopez-Calle,K.-H. Baringhaus, H. Glombik, A. Ehnsen, W. Kramer, *Angew. Chem.* **1996**, *108*, 2363; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2222; b) R. Boyce, G. Li, H. P. Nestler, T. Suenaga, W. C. Still, *J. Am. Chem. Soc.* **1994**, *116*, 7955.
3) P. A. Tempest, R. W. Armstrong, *J. Am. Chem. Soc.* **1997**, *119*, 7607.
4) R. Hirschmann, K. C. Nicolaou, S. Pietramico, J. Salvino, E. M. Lealy, W. C. Shakespeare, P. S. Spengler, P. Hamley, A. B. Smith, T. Reisine, K. Raynor, C. Donaldson, W. Vale, L. Maechler, R. M. Freidinger, C. D. Strader, *J. Am. Chem. Soc.* **1993**, *115*, 12550; see also: K. C. Nicolaou, J. I. Trujillo, K. Chibale, *Tetrahedron* **1997**, *53*, 8751.
5) T. Q. Dinh, C. D. Smith, X. Du, R. W. Armstrong, *J. Med. Chem.* **1998**, *41*, 981.
6) M. J. Sofia, R. Hunter, T. Y. Chan, A. Vaughan, R. Dulina, H. Wang, D. Gange, *J. Org. Chem.* **1998**, *63*, 2802.
7) T. Wunberg, C. Kallus, T. Opatz, S. Henke, W. Schmidt, H. Kunz, *Angew. Chem.* **1998**, *110*, 2620; *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 2503.
8) S. David, A. Thieffry, A. Veyrières, *J. Chem. Soc. Perkin Trans. 1* **1981**, 1796; S. David, S. Hanessian, *Tetrahedron* **1985**, *41*, 643.
9) J. Habermann, H. Kunz, *J. prakt. Chem.* **1998**, *340*, 233.
10) W. Steglich, B. Neises, *Angew. Chem.* **1978**, *90*, 556; *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 522.
11) R. U. Lemieux, K. B. Hendricks, R. V. Stick, J. James, *J. Am. Chem. Soc.* **1975**, *87*, 4056.
12) J. J. Ottvort, C. A. A. de van Boeckel, J. H. Koning, J. H. van Boom, *Synthesis* **1981**, 305.
13) **6a:** α anomer: $[\alpha]_D^{25}$ +47.6 (c 0.6, $CHCl_3$); 400 MHz-^{1}H-NMR ($CDCl_3$): δ 4.63 (d, 1H, $J_{1,2}$ = 3.5 Hz, 1-H), 4.31 (dd, 1H, $J_{3,2}$ = 7.0 Hz,$J_{3,4}$ = 5.3 Hz, 3-H), 4.16 (dd, 1H, $J_{4,5}$ = 2.5 Hz, 4-H), 0.89 (t, 3H, J = 7.3 Hz, CH_3, Prop). MALDI MS (DHB): *m/z* = 389.1 ($M+Na^+$).
7b: α : β > 7 : 1: 100.6 MHz-^{13}C-NMR ($CDCl_3$): δ 109.6 (CMe_2, α), 109.1 (CMe_2, β), 98.5 (C-1, β), 98.3 (C-1, α), 55.6 (O-CH_3, β), 55.5 (O-CH_3, α). Electrospray MS (pos.): *m/z* = 489.3 ($M+H^+$).
10b: α : β > 6 : 1: 100.6 MHz-^{13}C-NMR ($CDCl_3$): δ 169.1 (*C*OOtBu), 152.4 (broad, *C*ONHAr) 98.7 (C-1, β), 98.5 (C-1, α), 55.6 (O-CH_3, β), 53.7 (O-CH_3, α), 29.7 (CH_2COOtBu), 28.0 (CMe_3). Electrospray MS (pos.): *m/z* = 716.5 ($M+H^+$).
11a: α : β > 8 : 1: 100.6 MHz-^{13}C-NMR ($CDCl_3$): δ 156.8, 152.4, 152.0 (*C*=O) 98.6 (C-1, α), 55.5 (O-CH_3, α), 31.2 (CMe_3), 31.1 (CH_3). Electro spray MS (pos.): *m/z* = 779.8 ($M+Na^+$).