Pergamon

Tetrahedron Letters, Vol. 36, No. 50, pp. 9161-9164, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)02002-0

Synthesis of Novel Mimetics of the Sialyl Lewis X Determinant

Alexander Toepfer*[a], Gerhard Kretzschmar[a] and Eckart Bartnik[b]

a) Zentralforschung der Hoechst AG, G 830, D-65926 Frankfurt am Main
b) Pharmaforschung Hoechst AG, Werk Kalle-Albert, D-65174 Wiesbaden

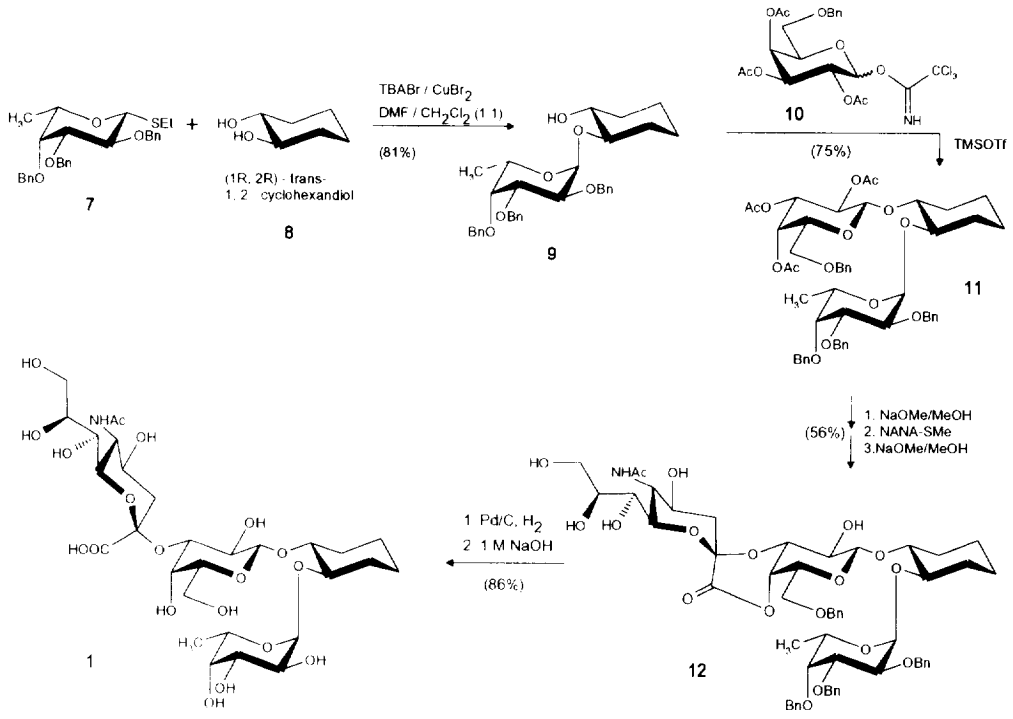
Abstract: Mimetics of the sialyl Lewis-X determinant in which at least one sugar domain is simulated by a di-, tri- or tetraalcohol unit have been synthesized. The inhibitory potency of these compounds for E- and P-selectin mediated cell adhesion has been evaluated in cell culture assays. The receptor binding affinity of the best of these mimetics was slightly higher than that of the natural oligosaccharide ligand sialyl Lewis X.

Adhesion of leukocytes to the activated endothelium of blood vessels plays an important role in inflammatory responses. This process is mediated by several adhesion molecules, particularly E- and P-selectin, which are believed to interact with sialyl Lewis X and its positional isomer sialyl Lewis A[1]. Blockade of this interaction may therefore provide novel therapeutics for the treatment of acute and/or chronic diseases in which excessive adherence of neutrophils occurs at inflamed tissue sites[2].

Sialyl Lewis X or A are frequently taken as the natural lead structures for the design of glycomimetics that structurally resemble and functionally mimic the natural oligosaccharide. These compounds, designed as selectin receptor antagonists, are currently being evaluated as potential anti-adhesive and anti-inflammatory drugs[3-6]. Sialyl Lewis X pentasaccharide has shown promising efficacy in animal models of acute inflammation of the lung[7] and of myocardial ischaemia and reperfusion injury[8].

Sialyl Lewis X, sialyl Lewis A as well as 3'-sialyl-3-fucosyl lactose[9] obviously can bind to E-selectin *via* a common epitope[9, 10]. For this reason we first substituted the GlcNAc domain by a (1R,2R)-*trans*-1,2-cyclohexandiol unit **8**. Because of the C_2-symmetry of **8** the resulting structure represents a mimetic for both sialyl Lewis X and sialyl Lewis A. This approach was also used by Prodger *et al.* who replaced the GlcNAc domain by the flexible 2,3-butanediol moiety[11], however no IC_{50} binding data were given.

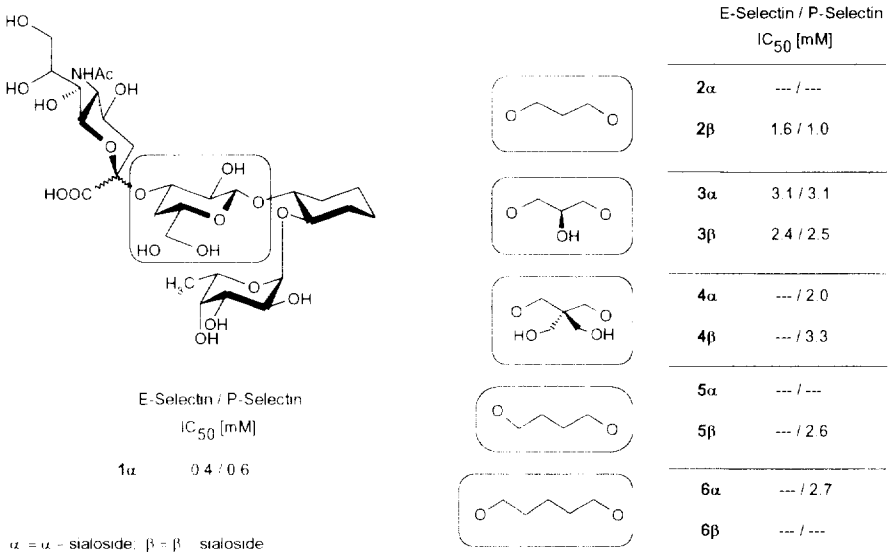
Due to the C_2-symmetry and the reduced number of functional groups the synthesis of mimetics **1-6** is much more convenient compared to that of sialyl Lewis X. The need for protecting groups is significantly reduced and the higher nucleophility of the hydroxyl groups of the template **8** (compared with those of GlcNAc) gives better yields in the glycosylation steps.



Scheme 1

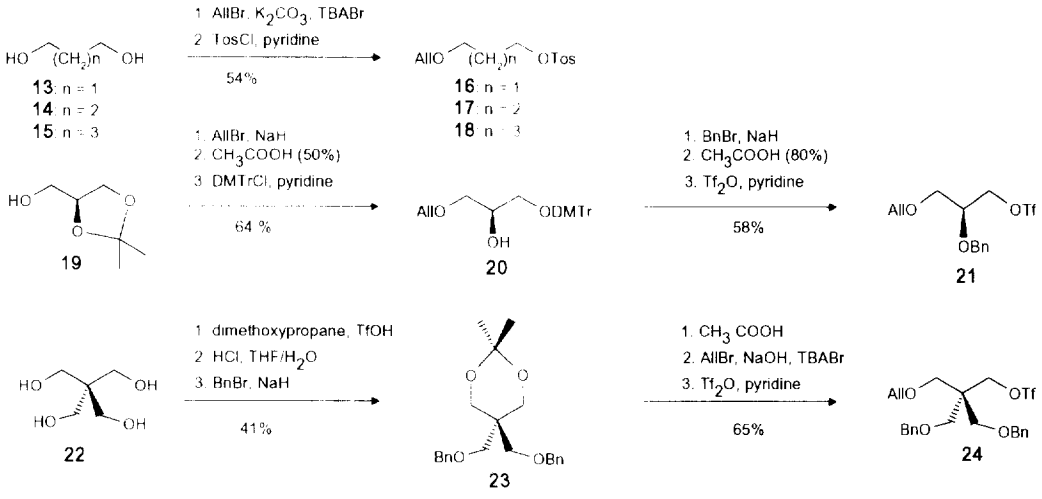
The synthesis of the fucoside **9** was accomplished by the reaction of one equivalent of the fucose donor **7**[12] with 1.5 equivalents of **8** in good yield. Intermediate **9** could be used directly for the next glycosylation[13] with the galactosyl donor **10**. The further steps to **1**[14] are straightforward, as shown in scheme 1.

For the synthesis of the even more simplified mimetics **2**[14]**-6** (scheme 2) in which the Gal domain is simulated by a polyalcohol moiety, the spacers **16-18**, **21** and **24** (scheme 3) were synthesized *via* standard methods.The building-up of the mimetics **2-6** is shown by way of the compounds **2α** and **2ß** (scheme 4). Compound **9** was first alkylated by the tosylate **16**. Then the allyl protecting group was cleaved and the resulting primary hydroxyl group was sialylated by methyl S-(methyl-5-acetamido-2,4,7,8,9-penta-O-acetyl-3,5-dideoxy-D-glycero-D-galacto)-2-nonulopyranosylonate[15]. The protecting groups of the resulting sialoside were cleaved to yield **2α** and **2ß**. The IC_{50}[16] of the new mimetics **1-6** are summarized in scheme 2. The IC_{50} of the reference compound sialyl Lewis X is about 1 mM for E-selectin and 2 mM for P-selectin. Besides compound **1**, in which the structure very closely resembles sialyl Lewis X, mimetic **2ß** exhibits good receptor affinities for E- and especially for P-selectin. This result is particularly surprising since the sialic acid moiety in **2ß** is in the ß-configuration[14]. In conclusion, the GlcNac domain can be substituted by a simple rigid structure without any

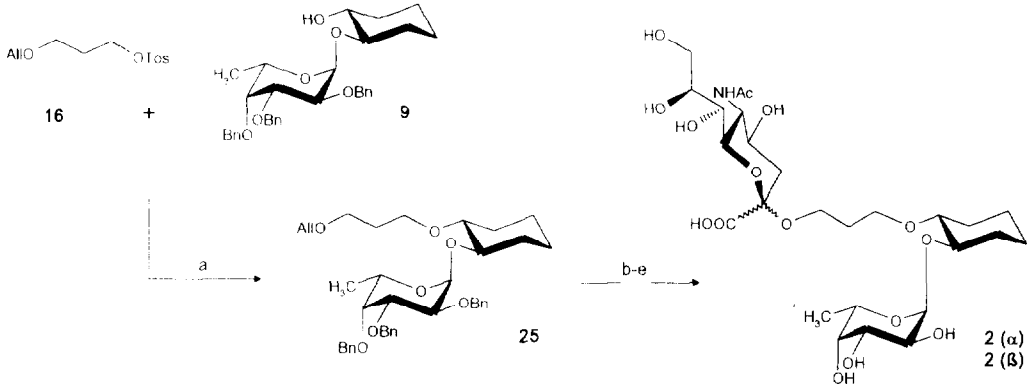


Scheme 2

loss of affinity to E- and P-selectin. The replacement of galactose by 1,3-propanediol only leads to good results by simultaneous change from the α- to the ß-sialoside. In this case the use of spacer moieties with additional hydroxyl groups, as suggested by Xiang *et al.*[17], resulted in higher IC_{50} values. Furthermore, mimetics with galactose substitutes longer than 1,3-propanediol (**5α/ß, 6α/ß**) led to unsatisfactory receptor affinities.



Scheme 3



a: NaH, DMF, 92% b: $[C_6H_5)_3P]RhCl$, 64% c: NANA-SMe, N-iodosuccinimide, TfOH, 44% (α-sialoside) + 32% (ß-sialoside)
d: NaOMe, 100% e: 1. PdC/H_2, 2. 1M NaOH, 86%

Scheme 4

References and Notes

1. (a) Springer, T. A. Nature, **1990**, *346*, 425. (b) Osborn, L. Cell, **1990**, *62*, 3.
2. Wong, C.-H. J. Org. Chem., **1995**, *60*, 3100 and references cited therein.
3. Dasgupta F., Rao B.N.N., *Exp.Opin.Invest.Drugs* **1994**, *3*, 709-724.
4. Stahl W., Sprengard U., Kretzschmar G., Kunz H. *Angew. Chem.* **1994**, *106*, 2186-2188; *Angew.Chem. Int.Ed.Engl.* **1994**, *33*, 2096-2098.
5. Stahl, W.; Sprengard, U.; Kretzschmar, G.; Bartnik, E.; Hüls, C.; Kunz, H. *J. Prakt.Chem.* **1995,** in press.
6. Sprengard U.; Kretzschmar G.; Bartnik E.; Hüls C.; Kunz H. *Angew.Chem.* **1995**, *107*, 1104-1107; *Angew.Chem.Int.Ed Engl.* **1995**, *107*, 990-993
7. Mulligan, M. S.; Paulson, J.C.; DeFrees, S.; Zheng, Z.-L.; Lowe, J.B.; Ward, P.A. *Nature* **1993**, *364*, 149-151.
8. Lefer, D.J.; Flynn, D.M.; Phillips, M.L.; Ratcliffe, M.; Buda, A.J. *Circulation* **1994**, *90*, 2390-2401.
9. Tyrrell, D.; James, P.; Rao, N.; Foxall, C.; Abbas, S.; Dasgupta, F.; Nashed, M.; Hasegawa, A.; Kiso, M., Asa, D., Kidd, J.,Brandley B. K. *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 10372.
10. (a) Lin, Y-C., Hummel, C.W.; Huang, D-H.; Ichikawa, Y.; Nicolaou, K. C.; Wong, C-H. *J. Am. Chem. Soc.* **1992**, *114*, 5452. (b) Ball, G. E.; O'Neill, R. A.; Schultz, J. E.; Lowe, J. B.; Weston, B. W.; Nagy, J. O.; Brown, E. G., Hobbs, C. J.; Bednarsky, M. D. *J. Am. Chem. Soc.* **1992**, *114*, 5449.
11. J. C. Prodger, M. J. Bamford, P. M. Gore, D. S. Holmes, V. Saez, P. Ward. *Tetrahedron Lett.* **1995**, 2339.
12. Yamazaki, F. Sato, S, Nukada, T., Ito, Y., Ogawa, T. *Carbohydr. Res.* **1990**, *201*, 31-50.
13. Schmidt, R. R. *Angew. Chem.* **1986**, *98*, 213-236; *Angew. Chem. Int. Ed. Engl.* **1986** *25*, 212-235.
14. ^{1}H-NMR (D_2O) **1α**: δ = 0.98 (d, 3H, 6-H_{fuc}), 1.04 (m, 4 H, 4-$H_{cyclohex}$, 5-$H_{cyclohex}$), 1.51, 1.93 (2 m, 4 H, 3-$H_{cyclohex}$, 6-$H_{cyclonex}$), 1.68 (dd, 1 H, 3-H_{nana}), 1.84 (s, 3 H, NAc), 2.55 (dd, 1 H, 3-H_{nana}), 3.94 (dd, 1 H), 4.38 (d, 1 H, 1-H_{gal}), 4.45 (m, 1 H, 5-H_{fuc}), 4.79 (d, 1 H, 1-H_{fuc}); **2α**: δ = 1.05 (d, 3H, 6-H_{fuc}), 1.65 (dd, 1 H, 3-H_{nana}), 1.86 (s, 3 H, NAc), 2.58 (dd, 1 H, 3-H_{nana}), 4.86 (d, 1 H, 1-H_{fuc}); **2ß**: δ = 1.05 (d, 3H, 6-H_{fuc}), 1.60 (dd, 1 H, 3-H_{nana}), 1.90 (s, 3 H, NAc), 2.25 (dd, 1 H, 3-H_{nana}), 4.87 (d, 1 H, 1-H_{fuc}).
15. Kanie, O.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1988**, *7*, 501-506.
16. IC_{50} values were determined as described by Kretzschmar, G.; Sprengard, U.; Kunz, H.; Bartnik, E.; Schmidt, W.; Toepfer, A.; Hörsch, B.; Krause M.; and Seiffge D. *Tetrahedron*, submitted **1995.**
17. Kaila, N., Yu, H-A., Xiang YB. *Tetrahedron Lett.* **1995**, 5503.

(*Received in Germany* 4 *September* 1995; *accepted* 17 *October* 1995)