Pergamon

Tetrahedron Letters 39 (1998) 3273–3276

TETRAHEDRON LETTERS

The Synthesis of Novel Structural Analogues of Sialyl Lewis^x

Paul V. Murphy,[a] Rod E. Hubbard,[a] David T. Manallack,[b] John G. Montana [b] and Richard J. K. Taylor [a,*]

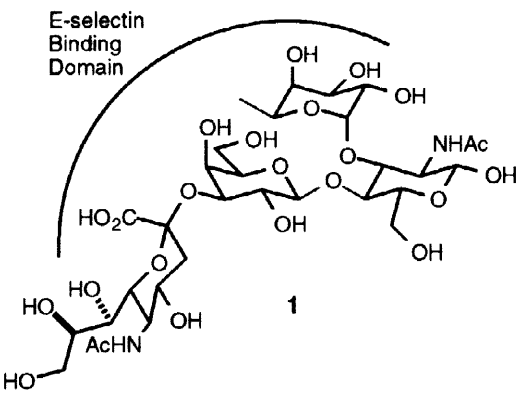
[a]Department of Chemistry, University of York, Heslington, York YO1 5DD, UK

[b]Chiroscience Limited, Cambridge Science Park, Milton Road, Cambridge CB4 4WE, UK

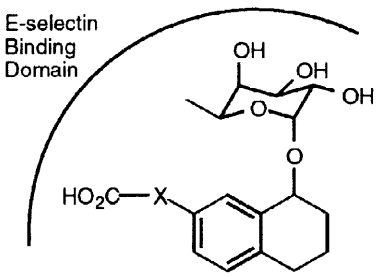
Received 17 December 1997; accepted 27 February 1998

Abstract: The synthesis of conformationally rigid tetralin-based mimics of the tetrasaccharide sialyl Lewis^x are described. Palladium catalysed coupling reactions are employed in the key synthetic steps.

Oligosaccharides have many important biological functions. Carbohydrate mediated adhesion of white blood cells (leukocytes) to the activated endothelium of blood vessels, for example, is an important event in the inflammatory response.[1] The Ca^{2+} dependent interaction between the E-selectin of endothelial cells and sialyl Lewis^x (sLe^x) (**1**) is a critical carbohydrate-protein recognition event in cell adhesion that leads to the migration of the white blood cells to sites of injury and infection. The recruitment of too many leukocytes can lead to damage of healthy tissue and thus to a number of immune system mediated diseases such as rheumatoid arthritis, reperfusion injury and psoriasis. Evidence also exists that E-selectin-sLe^x recognition may play a role in tumour metastasis.[1] Thus, analogues of sLe^x which inhibit the cell adhesion process could have potential as novel therapeutics for the treatment of inflammatory diseases and for the prevention of tumour metastasis.[1,2]



1



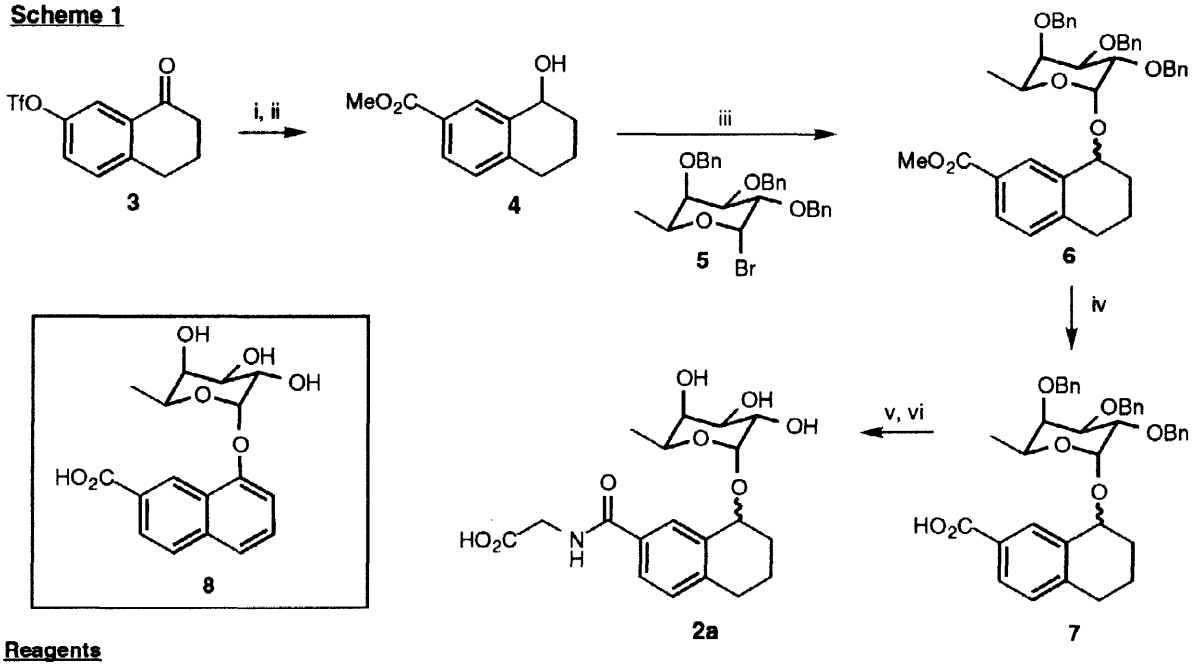
2a; X = CH_2NHCO
2b; X = $CH_2CH_2CH_2$
2c; X = $C(Me)_2C{\equiv}C$
2d; X = $C(Me)_2CH_2CH_2$

It has been shown that the minimum structural requirements for sLe^x binding to E-selectin are the carboxylic acid group of the sialic acid residue and the fucose hydroxyl groups, although the galactosyl 4- and 6-OH groups have also been implicated.[3] We describe the synthesis of novel analogues (**2a-d**) of sLe^x which contain these minimum binding requirements; the fucose residue and carboxyl group are held in an optimum position for selectin recognition by using an appropriately substituted, conformationally rigid, tetrahydronaphthalene ring system as a scaffold. Molecular modelling and biological studies of these and related compounds in relation to their binding to E-selectin will be discussed elsewhere.[4]

0040-4039/98/$19.00
PII: S0040-4039(98)00468-7

Palladium catalysed carbon-carbon bond forming reactions provided key intermediates for the synthesis of compounds (**2a-d**). The synthesis of the amino acid derivative (**2a**) was carried out first (Scheme 1). The aryl triflate (**3**) was easily prepared in two steps from commercially available 7-methoxy-1-tetralone as previously described.[5] Palladium catalysed carbonylation of (**3**) using palladium(II) acetate, 1,3-bis(diphenylphosphino)-propane (dppp) in DMF/MeOH, with triethylamine as base, followed by reduction of the resultant keto triflate with sodium borohydride gave the alcohol (**4**) in excellent overall yield. Halide ion catalysed glycosylation[6] of (**4**) using the bromide (**5**)[7] gave the fucoside (**6**) with high α-stereoselectivity as a 1:1 mixture of tetrahydronaphthalene diastereoisomers. Saponification of (**6**) using lithium hydroxide in aqueous THF gave acid (**7**) which was treated with glycine benzyl ester hydrochloride in the presence of the BOP-Cl coupling reagent and triethylamine[8] to produce, after debenzylation, the glycopeptide sLe^x mimetic (**2a**) in good yield. The spectroscopic data for (**2a**) were consistent with the proposed structure: the NMR spectra (270/67.5 MHz, D_2O:acetone-d_6) showed characteristic signals for the diastereoisomeric anomeric protons and carbons [δ_H 5.28 (1H, d, *J* 2.4Hz) and δ 5.21 (1H, d, 3.4Hz); δ_C 101.0 and δ 97.7]. Using similar methodology to that employed to make (**7**), naphthalene analogue (**8**) was prepared for biological evaluation.

Scheme 1

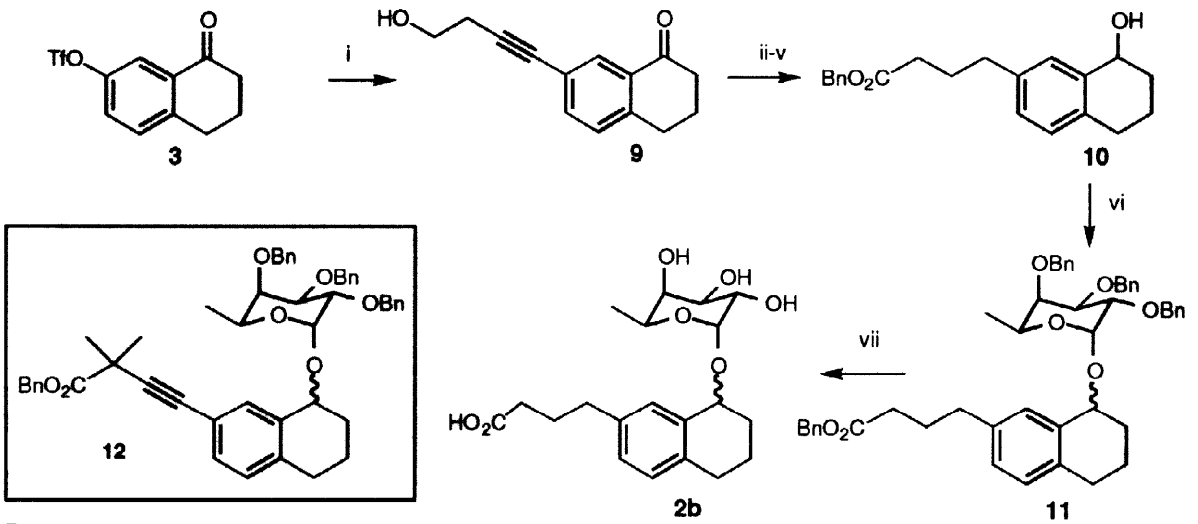


Reagents

(i) $Pd(OAc)_2$, CO, MeOH, DMF, NEt_3, dppp, 95%; (ii) $NaBH_4$, MeOH, 80%; (iii) Et_4NBr, CH_2Cl_2, mol. sieves, 61%; (iv) LiOH, THF:H $_2$O (4:1), 92%; (v) BOP-Cl, Et_3N, $BnO_2CCH_2NH_2.HCl$, CH_2Cl_2, 66%; (vi) H_2, 5% Pd-C, EtOH, 72%.

The aryl triflate (**3**) also proved to be a useful intermediate in the preparation of the alkyl linked analogue (**2b**) (Scheme 2). Palladium catalysed coupling of 3-butyn-1-ol with (**3**) gave the acetylene (**9**) in 77% yield. We found that the highest yields for this transformation were obtained when bis(triphenylphosphine)palladium(II) chloride was used to effect the transformation in DMF with triethylamine as base.[9] The acetylene (**9**) was converted into the alcohol (**10**) in four steps (alkyne hydrogenation, oxidation of alcohol to carboxylic acid using Jones' reagent, esterification with DCC/DMAP and benzyl alcohol, ketone reduction). Fucosylation of (**10**) using the bromide (**5**) as described above gave the α-anomer (**11**) as a 1:1 mixture of tetrahydronaphthalene diastereoisomers in 42% yield. Compound (**2b**) was obtained in 71% yield when the benzyl groups were removed from (**11**) by catalytic hydrogenation using 5% palladium on activated carbon in ethanol.

Scheme 2

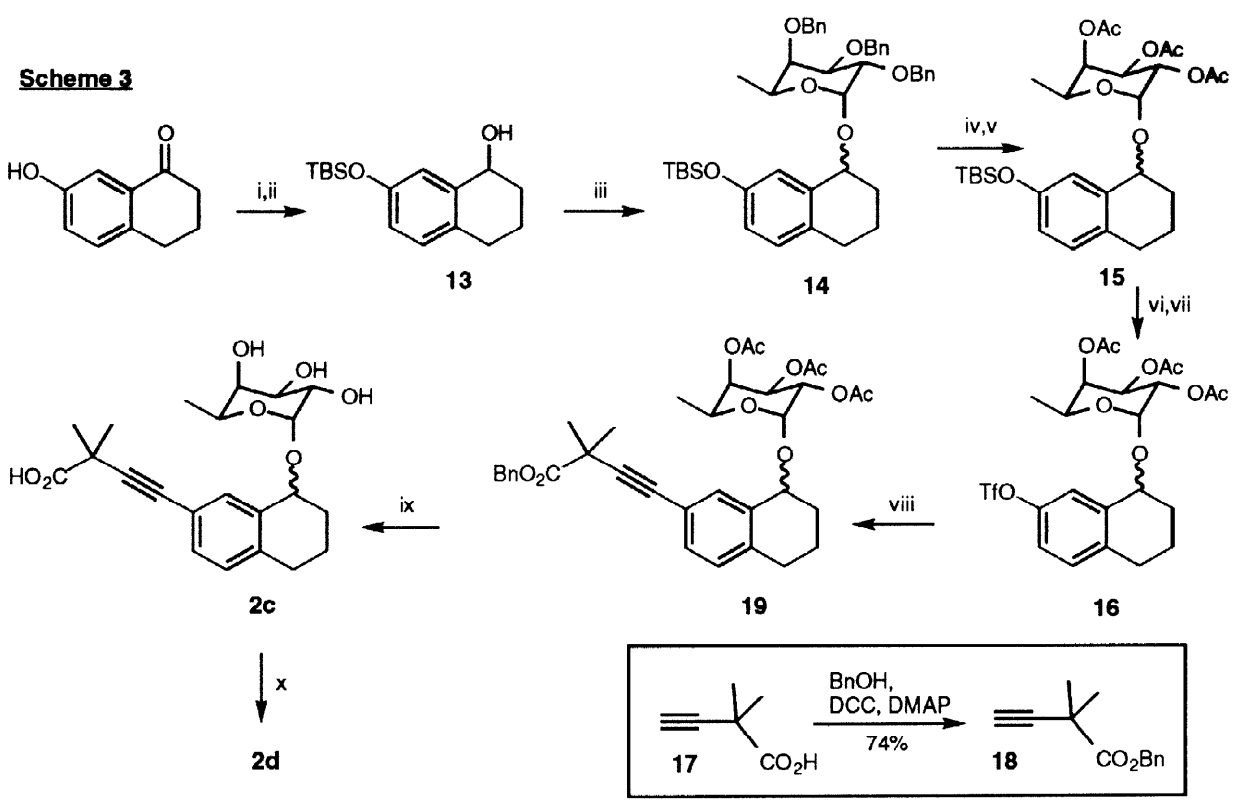


Reagents

(i) $PdCl_2(PPh)_3$, 3-butyn-1-ol, DMF, Et_3N, 77%; (ii) 5% Pd-C, H_2, EtOH, 96%; (iii) Jones' Reagent, acetone, 61%; (iv) BnOH, DCC, DMAP, CH_2Cl_2, 88% ; (v) $NaBH_4$, MeOH, 78%; (vi) (5), Et_4NBr, CH_2Cl_2, mol. sieves, 42%; (vii) 5% Pd-C, H_2, EtOH, 71%.

We were also interested in preparing analogues of (**2b**) which contain a multiple bond in the acid side chain. We first attempted to utilise the chemistry shown in Scheme 2 to prepare the alkyne (**2c**). Thus, precursor (**12**) was prepared without difficulty but we were unable to debenzylate (**12**) using H_2-Pd without reducing the alkyne.[10]

Scheme 3



Reagents

(i) TBSCl, Im., DMF, 92%; (ii) $NaBH_4$, MeOH, 77%; (iii) (5), Et_4NBr, CH_2Cl_2, mol. sieves, 73%; (iv) 5% Pd-C, H_2, EtOH; (v) Ac_2O, Py., 91% over 2 steps; (vi) TBAF, THF; (vii) Tf_2O, 2,6-lutidine, DMAP (cat.), CH_2Cl_2, 79% over 2 steps; (viii) $PdCl_2(PPh)_3$, (**18**), DMF, Et_3N, 56%; (ix) NaOMe, MeOH, then LiOH, H_2O, 55%; (x) 5% Pd-C, H_2, 95%.

We therefore developed the sequence shown in Scheme 3 for the preparation of unsaturated analogues; it is noteworthy in that the palladium coupling reaction is carried out on the preformed fucoside (**16**). Thus, the t-butyldimethylsilyl (TBS) derivative (**13**) was prepared in two steps from 7-hydroxy-1-tetralone[5] and on reaction with the bromide (**5**) gave the α-fucoside (**14**) as a 1:1 mixture of diastereoisomers. Removal of the benzyl groups was effected by hydrogenation and the fucose hydroxyl groups were protected by acetylation using acetic anhydride in pyridine giving (**15**). The TBS group of (**15**) was removed with TBAF in THF and subsequent reaction of the product with trifluoromethanesulfonic anhydride in the presence of 2,6-lutidine and catalytic DMAP gave the triflate (**16**). Palladium catalysed coupling of (**16**) with acetylene (**18**) [prepared by esterification of acid (**17**)[11]] gave (**19**). When (**19**) was treated with catalytic sodium methoxide in methanol followed by LiOH the sLe^x analogue (**2c**) was obtained in 50% yield over two steps. Hydrogenation of (**2c**) gave (**2d**), which was also obtained by debenzylation-hydrogenation of alkyne (**12**).

Compound (**2b**) proved to be the most potent of these compounds, and more potent than sLe^x itself, with 90% inhibition of adhesion of resting HL60 cells on TNFα-stimulated HUVEC at 1.0 *mM* concentration (sLe^x has 50% inhibition at 1.0 *mM*).[4]

In summary, we have completed the synthesis of novel, conformationally constrained analogues of sialyl $Lewis^x$ utilising palladium catalysed coupling reactions in key synthetic steps. Triflate (**16**) is a potentially useful intermediate for the synthesis of a range of alkene and alkyne analogues and we are currently exploring this chemistry in order to establish structure-activity relationships.[12,13]

References and Notes

1. Roy, R. pp 85-135 and Hasegawa, A.; Kiso, M. pp 137-155 in *Carbohydrates in Drug Design,* Ed. Witczak, Z. J.; Nieforth, K. A. Marcel Dekker, New York, 1997 and references therein.
2. For recent examples see Wong, C. H.; Moris-Varas, F.; Hung, S.-C.; Marron, T. G.; Lin, C.-C.; Gong, K. W.; Weitz-Schmidt, G. *J. Am. Chem. Soc.* 1997, **119**, 8152; Hanessian, S.; Reddy, G. V.; Huynh, H. K.; Pan, J.; Padatella, S. *Bioorg. Med. Chem. Lett.* 1997, **7**, 2729; Kolb, H. C.; *Bioorg. Med. Chem. Lett.* 1997, **7**, 2485; Toepfer, A.; Kretzschmar *Bioorg. Med. Chem. Lett.* 1997, **7**, 1311; Huang, B.-G.; Locke, R. D.; Jain, R. K.; Matta, K. L. *Bioorg. Med. Chem. Lett.* 1997, **7**, 1157; Miyauchi, H.; Yuri, M.; Tanaka, M.; Kawamura, N.; Hayashi, M. *Bioorg. Med. Chem. Lett.* 1997, **7**, 985; Bänteli, R.; Ernst, B. *Tetrahedron Lett.* 1997, **38**, 4059.
3. Uchiyama T.; Vassilev, V. P.; Kajimoto, T.; Wong, W.; Huang,W.; Liu, C. C.; Wong C. H. *J. Am. Chem. Soc.* 1995, **117**, 5395.
4. Murphy, P. V.; Manallack, D. T. ; Hubbard, R. E.; Montana, J. G.; Taylor, R. J. K. Manuscript in preparation.
5. Gerlach, U.; Wollmann, T. *Tetrahedron Lett.* 1992, **33**, 5499.
6. Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* 1975, **97**, 4056.
7. Lonn, H. *Carbohydrate Res.* 1985, **139**, 105.
8. Cabre, J.; Palomo, A. L. *Synthesis* 1984, 413.
9. Chen, Q. Y.; Yang, Z-Y. *Tetrahedron Lett.* 1986, **27**, 1171.
10. Other methods (Na/NH_3, $FeCl_3$, TMSI, $BCl_3.SMe_2$) were investigated in an attempt to deprotect benzyl ethers such as (**12**) but these reactions gave complex product mixtures. See Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis,* 2nd Ed., Wiley and Sons, New York, 1991, p. 49.
11. Schexnayder, M. A.; Engel, P. S. *J. Am. Chem. Soc.* **97**, 1975, 4828.
12. Where relevant, compounds were characterised as 1:1 mixtures of diastereoisomers. All novel compounds were characterised by NMR spectroscopy and elemental analysis and/or high resolution mass spectrometry.
13. Taylor, R. J. K.; Murphy, P. V.; Montana, J. G.; Manallack, D. T. U. K. Patent Application No. 9618520.2 (5.9.96).