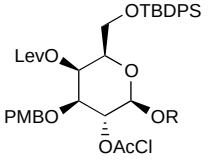
Oligosaccharide libraries

This column has frequently featured approaches to oligosaccharide libraries, mainly because these products are important pharmacological agents, but also because the synthesis of oligosaccharides poses significant problems. A recent paper from The Scripps Research Institute describes a useful orthogonal protection strategy that extends the accessibility of oligosaccharide libraries made in solution [Wong C-H. *et al. J. Am. Chem. Soc.* (1998) 120, 7137–7138].

The key advance described in this paper is an effective orthogonal protection–deprotection strategy that allows



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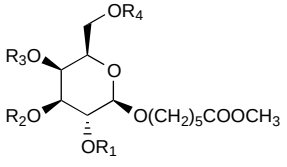

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the sequential removal of four different protecting groups from a core building block (**3**). Each of the four hydroxyls is protected by a different group: chloroacetyl (ClAc), *p*-methoxybenzyl (PMB), levulinyl (Lev), and *t*-butyldiphenylsilyl (TBDPS) selectively removed by sodium bicarbonate, trifluoroacetic acid, hydrazine and hydrogen fluoride-pyridine, respectively. After each deprotection the hydroxyl revealed can be coupled with a choice of seven glycosyl donors to generate 56 disaccharides, 1176 trisaccharides and, ultimately, 38,416 pentasaccharides.

This strategy has been used to prepare 45 protected oligosaccharides (**4**) in multimilligram amounts. Work is in progress to increase the number of compounds synthesized and screen for compounds that bind to lectins and antibodies.

Nick Terrett
Discovery Chemistry
Pfizer Central Research
Sandwich, Kent, UK
fax: +44 1304 618422
e-mail: nick_terrett@sandwich.pfizer.com

Emerging molecular targets

Caspase-8: an initiator of Fas-mediated apoptosis

Apoptosis – programmed cell death – is responsible for most cell deaths observed during embryogenesis, metamorphosis and normal tissue turnover. During apoptosis, protein-degrading enzymes known as caspases are activated and cleave critical cellular substrates leading to the ultimate death of the cell. The caspases are produced as inactive precursors that must themselves be activated by other caspases, so there is a cascade of cleavage and activation to induce apoptosis. In the immune system, the Fas molecule is a key inducer of the apoptotic process.

A recent paper by a group from Harvard Medical School describes an investigation into a human T-cell line variant found to be resistant to Fas-induced apoptosis [Juo, P. *et al. Curr. Biol.* (1998) 8, 1001–1008]. Examination of the cells for all the molecules known to be involved in Fas-induced apoptosis showed that the variant lacked the expression of caspase-8 but that all the other proteins were found to be present at normal levels. The group also showed that reintroduction of caspase-8 into these cells restored their sensitivity to Fas-mediated apoptosis. This implicates caspase-8 as the key enzyme responsible for the initiation of apoptosis in Fas-triggered cell death.

As malfunctions in the Fas system are involved in a variety of diseases, caspase-8 inhibitors or activators may have therapeutic potential for the correction of Fas-pathway defects.

Lymphoid sulphotransferase

During the inflammatory process, lymphocytes migrate from the bloodstream into the tissues by adhering to the endothelial cells lining specialized blood vessels. The process of adhesion is mediated through the binding of L-selectin on the surface of the lymphocytes to glycoproteins on the endothelial cell surface. Previous studies have shown that L-selectin binding requires sulphation of the endothelial surface glycoproteins but, until now, the identity of the sulphotransferase enzyme responsible for this process has been unknown.

Bertozzi's group has recently reported the identification of an enzyme specific to lymphoid tissue that can sulphate synthetic glycoprotein analogues, and suggest that this enzyme may be responsible for sulphation of glycoproteins recognized by L-selectin [Bowman, K.G. *et al. Chem. Biol.* (1998) 5, 447–460]. In addition to providing an insight into the mechanism of lymphocyte homing, the identification of this enzyme may lead to useful therapeutic agents for inflammatory control.

Andrew Lloyd

Bioinformatics

Integrated approach to bioinformatics

The tremendous pace of biomedical science is leading to an 'information explosion', an increased dependency on computers and an absolute need for effective and efficient use of bioinformatics. Bioinformatics is essential for the management and analysis of biological information and serves to eliminate *ad hoc* planning, enable informed decision-making, provide relevant information and mobilize all available biological information to take the discovery process forward and produce commercially viable products and patents. Consequently, up-to-date and rapid access to the right information (computer databases) and the right analytical tools (computer programs)

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