The formation of hydrophilic, but not necessarily ionizable, glycolamide esters has been utilized by Bundgaard and Nielsen (1987, 1988) to generate prodrugs of carboxylic acid-bearing agents, including nonsteroidal anti-inflammatory drugs. The esters possess a high susceptibility to enzymatic hydrolysis and a high stability in aqueous media. *N,N*-disubstituted 2-hydroxyacetamide is the promoiety that is readily cleaved at 37°C in 80% human plasma in pH 7.4 phosphate buffer. The two substituents on the amide nitrogen are the most important structural features for rapid hydrolysis by plasma enzymes, but it is also these substituents that can allow the desired solubility or lipophilicity to be readily achieved. When this approach was taken with furosemide, the hydrolysis rate in human plasma was slow (Mørk et al., 1990). The authors suggest that the furfuryl amino group in the *ortho*-position of these furosemide esters could be contributing steric hindrance to enzymatic approach. Interestingly, esters of naproxen demonstrating different solubility and lipophilicity characteristics were each hydrolyzed with a half-life of less than 2 min in human plasma (Bundgaard and Nielsen, 1988). Preliminary studies have also revealed that the glycolamide esters of naproxen are completely absorbed following oral administration, and yet only the parent drug is detected in the plasma (Bundgaard and Nielsen, 1987).

Water-soluble intermediates to prodrugs of paclitaxel were prepared by transacylation reactions with divinyl adipate at the 2′-hydroxyl that were regioselectively catalyzed by thermolysin, since no other hydroxyl group on paclitaxel was esterified (Khmelnitsky et al., 1997). The vinyl group of this intermediate was then hydrolyzed in acetonitrile containing 1% water using *Candida antarctica* lipase to yield paclitaxel 2′-adipic acid (Table 16.1). Alternatively, the intermediate was used as the acyl donor in a dry reaction with glucose in acetonitrile, again catalyzed by *Candida antarctica* lipase, to yield paclitaxel 2′-adipoylglucose. It was assumed that the glucose was derivatized at the primary alcohol since enzymes of this sort have shown a high degree of selectivity for the primary alcohol of monosaccharides in such transesterification reactions (Therisod and Klibanov, 1986; Martin et al., 1992). Paclitaxel 2′-adipoylglucose and paclitaxel 2′-adipic acid exhibited markedly enhanced solubility that are, respectively, 58- and 1625-fold the solubility of paclitaxel itself (<4 μg/mL) (Khmelnitsky et al., 1997).

Since the sensitivity of the promoiety to acid conditions can be enhanced to effectively target drugs to solid tumors (Niethammer et al., 2001), an acid-sensitive paclitaxel prodrug was prepared. By taking advantage of the 2′ and 7 hydroxyl groups, a bifunctional carbonate intermediate could be formed by condensation with 2,2′-dimethyl-1,3-dioxolane-4-methanol chloroformate (the so-called solketal chloroformate). The intermediate was hydrolyzed to remove the 2′-carbonate and open the acetal ring to form a 7-(2″,3″-dihydroxypropyl carbonoxy) paclitaxel. Carbonates of paclitaxel with hydrophilic functional groups were reported to be more soluble in water and inert to tubulin (Nicolaou et al., 1993). This prodrug is activated under acidic conditions by hydrolytic cleavage of the carbonate to produce paclitaxel, carbon dioxide, and dihydroxypropanol. The prodrug solubility was tested by sonication in room temperature water for 15 min, and proved to be $8.7 \times 10^{-4}$ M, which is 58 times the $1.5 \times 10^{-5}$ M solubility of paclitaxel. In addition, the prodrug was found to be chemically stable for at least 24 h at ambient temperature in its proposed formulation for IV infusion, with less than 5% degradation after 48 h (Niethammer et al., 2001). A recent review of acid-sensitive anticancer drug–polymer conjugates includes a discussion of advances in the development and study of macromolecular drug delivery systems, ranging from simple polymer–drug conjugates to site-specific antibody-targeted conjugates (Ulbrich and Subr, 2004).

Replacement of an acidic NH proton with a methyl group is not an acceptable means to produce a prodrug because it is a permanent modification, and it can significantly affect the pharmacological properties of the parent drug (Bansai et al., 1981b). It has been recommended that the NH proton be replaced by a hydroxymethyl group by a simple and facile reaction with formaldehyde. The hydroxymethyl group is readily cleaved in water to return formaldehyde as a product (Alexander et al., 1988). (The positioning of a similar functional group at that site can be achieved by reaction of the parent drug with an appropriate aldehyde.) The hydroxymethyl group, of course, then offers the opportunity for ester prodrug development by reaction with a carboxylic acid-bearing promoiety,