used in patients with type 2 penicillin or cephalosporin hypersensitivity. There exists a nebulized formulation useful for cystic fibrosis patients colonized by Gram-negative rods, including *P. aeruginosa* (Gomez et al. 2015).

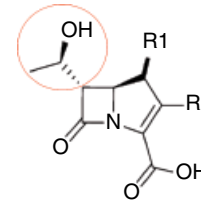

Figure 3.6 Carbapenem core structure. Circle: 6-*trans*-hydroxyethyl group.

3.3.4 Carbapenems

Carbapenems are the widest spectrum antibiotics available among beta-lactam agents. They differ from other beta-lactams in that they have a carbon atom instead of a sulfur or oxygen atom in the bicyclic nucleus and a hydroxyethyl side chain in *trans* configuration at position 6 (Figure 3.6), which confers stability against most beta-lactamases.

The first carbapenem known was thienamycin, produced by the Gram-positive bacteria *Streptomyces cattleya* (Birnbaum et al. 1985). Imipenem was subsequently obtained by chemical modification. In total, there are four carbapenems that are widely commercialized (doripenem, ertapenem, imipenem, and meropenem) and other two (biapenem and tebipenem) available only in Japan (Bush and Bradford 2016).

In general, their spectrum of activity extends to the majority of Gram-positive and Gram-negative pathogens, including both aerobes and anaerobes, due to their efficient bacterial penetration, stability against hydrolysis by most beta-lactamases, and high affinity for multiple PBPs. However, this class of beta-lactams shows intrinsic inactivity against methicillin-resistant staphylococci, *Enterococcus faecium*, and some non-fermenting rods, such as *Stenotrophomonas maltophilia* and *Burkholderia cepacia*.

Imipenem and doripenem are potent antibiotics against Gram-positive bacteria, whereas meropenem and ertapenem are slightly more effective against Gram-negative organisms. However, ertapenem has a more limited spectrum, because it is not as active as imipenem or meropenem against *P. aeruginosa* and other non-fermenting rods (Papp-Wallace et al. 2011).

3.3.5 Beta-Lactam Associated with Beta-Lactamase Inhibitors

Beta-lactamase inhibitors in clinical medicine are introduced in 1970 and are a good approach to combat beta-lactam resistance. They are used in combination with a beta-lactam and are able to restore the activity of beta-lactam.

They can be classified in two groups (Table 3.1):

- Beta-lactam inhibitors. Clavulanic acid, tazobactam, and sulbactam are structurally beta-lactams and act as inactivators or "suicide inhibitors" of class A beta-lactamases.