

ABSTRACT

The overall approach in the present investigation has been to explore applications of the Morita-Baylis-Hillman (MBH) reaction in asymmetric synthesis and in the construction of complex systems with medicinal potential. To this end, a series of varied camphor-derived acrylate esters was prepared to serve as chiral substrates in asymmetric Morita-Baylis-Hillman reactions. Reduction of *N*-substituted camphor-10-sulfonamides afforded the 3-*exo*-hydroxy derivatives as the major products. Acylation of the corresponding sodium alkoxides gave the desired 3-*exo*-acrylate esters, isolation of which was complicated by concomitant formation of hydrochlorinated and diastereomeric competition products. Bulky camphorsulfonamides containing alkyl, dialkyl, aromatic and adamantyl groups were selected as *N*-substituents with the view to achieving stereoselective outcomes in subsequent MBH reactions. The synthesis of the camphor-derived Morita-Baylis-Hillman adducts using various pyridine-carboxaldehydes proceeded with exceptionally high yields and with diastereoselectivities ranging from 7-33% d.e. Both 1D- and 2D-NMR and HRMS techniques were employed to confirm the structures and an extensive study of the electrospray MS fragmentation patterns of a number of camphor-derived chiral acrylate esters was conducted.

Attention has also been given to the application of MBH methodology in the construction of heterocyclic 'cinnamate-like' AZT conjugates, which were designed to serve as dual-action HIV-1 integrase-reverse transcriptase (IN-RT) inhibitors. A number of pyridine carboxaldehyde-derived MBH adducts were synthesized using methyl, ethyl and *t*-butyl acrylates in the presence of 3-hydroxyquinuclidine (3-HQ) as catalyst. The yields for these reactions were excellent, and the MBH adducts were acetylated and then subjected to aza-Michael addition using propargylamine – a reaction accompanied by loss of acetate in what is effectively an S_N' process. The resulting alkylamino compounds were then used as substrates in 'Click reactions' to form the targeted AZT-conjugates in moderate to excellent yield. *In silico* docking of computer-modelled AZT-conjugates into the HIV-1 integrase and reverse transcriptase enzyme-active sites was undertaken and potential hydrogen-bonding interaction with active-site amino acid residues were identified. The electrospray MS fragmentations of the AZT and the novel AZT-conjugates were also investigated and common fragmentation pathways were identified.