Abstract

Towards ensuring the enantiomerically pure synthesis of chiral molecules of biological as well as synthetic interest, using chiral molecules obtained from the chiral pool, the structure and stereochemistry of (2S, 3S) and (2S, 3R)-tetrahydro-3-hydroxy-5-oxo-2, 3- furan dicarboxylic acids (garcinia and hibiscus acids) isolated from locally available plant sources have been reinvestigated with the help of chiroptical techniques namely ORD, ECD and VCD simultaneously for the first time. The ECD, ORD, and VCD spectra of dimethyl esters of garcinia and hibiscus acids in solution phase have been subjected to a systematic analysis by comparing with the corresponding spectra predicted by quantum chemical methods. These observations underscore the importance of including solvent effects in quantum chemical calculations of chiroptical spectroscopic properties. Also it has been noted that none of these three (ECD, ORD, or VCD) spectroscopic methods, in isolation, can unequivocally establish the absolute configuration of diastereomers. This deficiency is eliminated when a combined spectral analysis of either ECD and VCD or ORD and VCD methods are used.

Having a six carbon skeleton with unique structure and stereochemistry, these γ-butyrolactone containing molecules have been employed for the successful synthesis of six carbon chiral building blocks namely the enantiopure concave bislactone skeleton (3aR, 6aS)-3a-hydroxytetrahydrofuro [3, 4-b] furan- 2,6-dione, an analogue of antifungal (+)-avenaciolide; methyl (2S)- hydroxyl [(3R)-3-hydroxy-5-oxotetrahydrofuran-3-yl] ethanoate, an intermediate for sesquiterpene lactones; (2S)-N-benzyl-2-hydroxy-2-[(3R)-3-hydroxy-5-oxotetrahydrofuran-3-yl]ethanamide, an intermediate for preparing the inhibitors of PNP and UDP-gal transferase enzymes; dimethyl (5S)-4-(2-methoxy-2-oxoethyl)-2-(trichloromethyl)-1,3-dioxolane-4,5-dicarboxylate and (2R,3R)-3-hydroxymethyl-pentane- 1,2,3,5-tetraol, a precursor for chiral phosphine ligand. Attempts were also made for the synthesis of (4R)-4-[(1R)-1,2-dihydroxyethyl]-4-hydroxydihydrofuran-2(3H)-one, (2S,3R)-3-hydroxy-3-(((4-methylphenyl)sulfonyl)oxy)methyl)-5-oxotetrahydrofuran-2-carboxylate and dimethyl (2S,3S)-3-hydroxy-4-ethyl-5-oxotetrahydrofuran-2,3-dicarboxylate, intermediates suited for the synthesis of irregular sesquiterpene lactones, funebrine and cinatrins respectively.
Boron reagents have been precisely tuned for cumulating the syntheses of such intermediates by the chemical modification of garcinia and hibiscus acids. A systematic selective (site as well as chemo) carbonyl reductions of the dialkyl \((2S, 3S)\) and \((2S, 3R)\) –tetrahydro-3-hydroxy -5-oxo-2, 3-furandicarboxylates, were carried out using borane-dimethyl sulfide (BMS) and catalytic amount of sodium borohydride at 0 °C. Under these conditions dialkyl \((2S, 3S)\)–tetrahydro-3-hydroxy -5-oxo-2, 3-furandicarboxylates yielded alkyl \((2S, 3R)\)-terahydro-3-hydroxy-3-hydroxymethyl-5-oxo-furan-2-carboxylate, in an extremely selective manner. However, the diasteromeric esters, dialkyl \((2S, 3R)\)–tetrahydro-3-hydroxy -5-oxo-2, 3-furandicarboxylates underwent the simultaneous reduction of the distal and proximal ester carboxylates afforded a mixture of polyhydroxy compounds with BMS and catalytic amount of sodium borohydride. This discriminative reduction of diastereomeric esters using BMS catalyzed by sodium borohydride clearly indicates the preferential involvement of intermediates in the reduction process. To clearly understand the possible intermediates responsible for the discrimination using BMS catalyzed by sodium borohydride reduction of dialkyl \((2S, 3S)\) and \((2S, 3R)\) –tetrahydro-3-hydroxy -5-oxo-2, 3-furandicarboxylates (α-hydroxy esters), a \(^{11}\text{B}\) NMR spectroscopic study has been undertaken for the first time. The study revealed the involvement of a transient alkoxy-BH\(_2\) (RO-BH\(_2\)) intermediate initially and its subsequent rapid, uncatalyzed transfer of a hydride to the proximal ester carbonyl to give a dialkoxyborane intermediate at 25 °C. Both sodium borohydride and sodium methoxide can catalyze hydride transfer from dialkoxyborane intermediates to the final trialkoxyborane derivatives which afforded the selective reduction product on quenching with methanol. Alternatively, the dialkoxyborane intermediates have been quenched with methanol to the corresponding α-hydroxy aldehyde. Also attempts have been made to isolate the aldehyde as bisulfite adducts. On the other hand, sodium borohydride in methanol at 0 °C behaved very similar to that of lithium aluminum hydride and reduced tandemly both the lactone and ester carbonyls of both garcinia and hibiscus esters.

**Key words:** Hydroxycitric acids, γ-butyrolactone, (+)-Avenaciolide, Sesquiterpene lactones, Hydroxy pyrrolidines, Funebrin, Cinatrins, VCD, ECD, ORD, \(^{11}\text{B}\) NMR spectroscopy, BMS, Sodium borohydride.