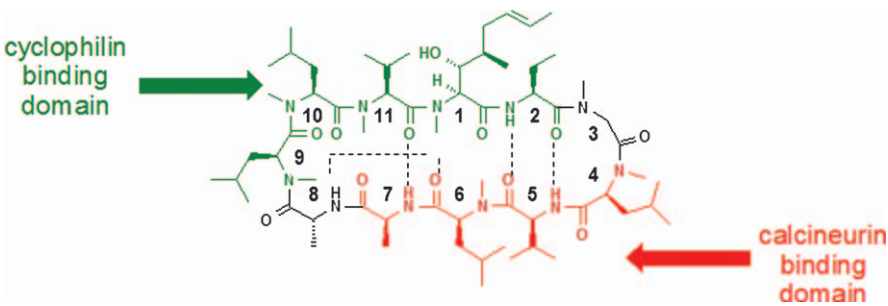
11.1.2 Cyclosporine A

11.1.2.1 Structure and Conformational Flexibility

Cyclosporine [also known as cyclosporin, cyclosporin(e) A and CsA; **1**, Figure 11.3] is a cyclic undecapeptide first isolated from the fungus *Tolypocladium inflatum* in 1970.[22] Throughout the literature, the structure of CsA, first elucidated in 1976,[23,24] is typically drawn as some variant of that shown in Figure 11.3, with each amino acid numbered 1 through 11 in a clockwise manner starting at 12 o'clock. Ten of the 11 amino acids are known or derivatives of known amino acids, with several having branched lipophilic side chains: 4 × Leu; 2 × Val, 2 × Ala, 1 × Gly (Sar) and 1 × Abu (aminobutyric acid). One of the 11 amino acids is previously unknown: Bmt or (4*R*)-4-[(*E*)-2-butenyl]-4-methyl-L-threonine. All 11 amino acids have the natural L-configuration except for [D-Ala][8] and the achiral [Sar][3]. Seven of the 11 amide nitrogens are capped with a methyl group.

Cyclosporine adopts different conformations depending on the polarity of the solvent in which it is dissolved.[25] In crystalline form and in non-polar solvents such as chloroform or THF, the hydrogens on the four uncapped amide nitrogens form intramolecular hydrogen bonds with the carbonyl oxygens of other amides within the molecule, as shown in Figure 11.3; three of these are transannular ([Abu][2]NH–[Val][5]C=O; [Val][5]NH–[Abu][2]C=O and [Ala][7]NH–[MeLeu][11]C=O), while the fourth is in a γ-turn ([D-Ala][8]NH–[MeLeu][6]C=O). Residues 1–6 adopt an antiparallel β-pleated sheet conformation, while residues 7–11 form an open loop featuring a *cis* amide bond between [MeLeu][9] and [MeLeu][10].[26] It is noted that this stable conformation is unique to CsA and close analogs; many synthetic derivatives disrupt this internal hydrogen-bonding network and exist as multiple conformers in non-polar solvent. Examples include derivatives that possess an L-substituent at [Sar][3],[27,28] and derivatives that are N-capped at the [Val][5] nitrogen.[29] This has a consequence to the biological activity of CsA analogs that is discussed in Section 11.3.



(1)

Figure 11.3 Structure of cyclosporine A (CsA) with the cyclophilin (green) and calcineurin (red) binding regions indicated. Key intramolecular hydrogen bonds that exist in non-polar solvents are indicated by dashed lines.