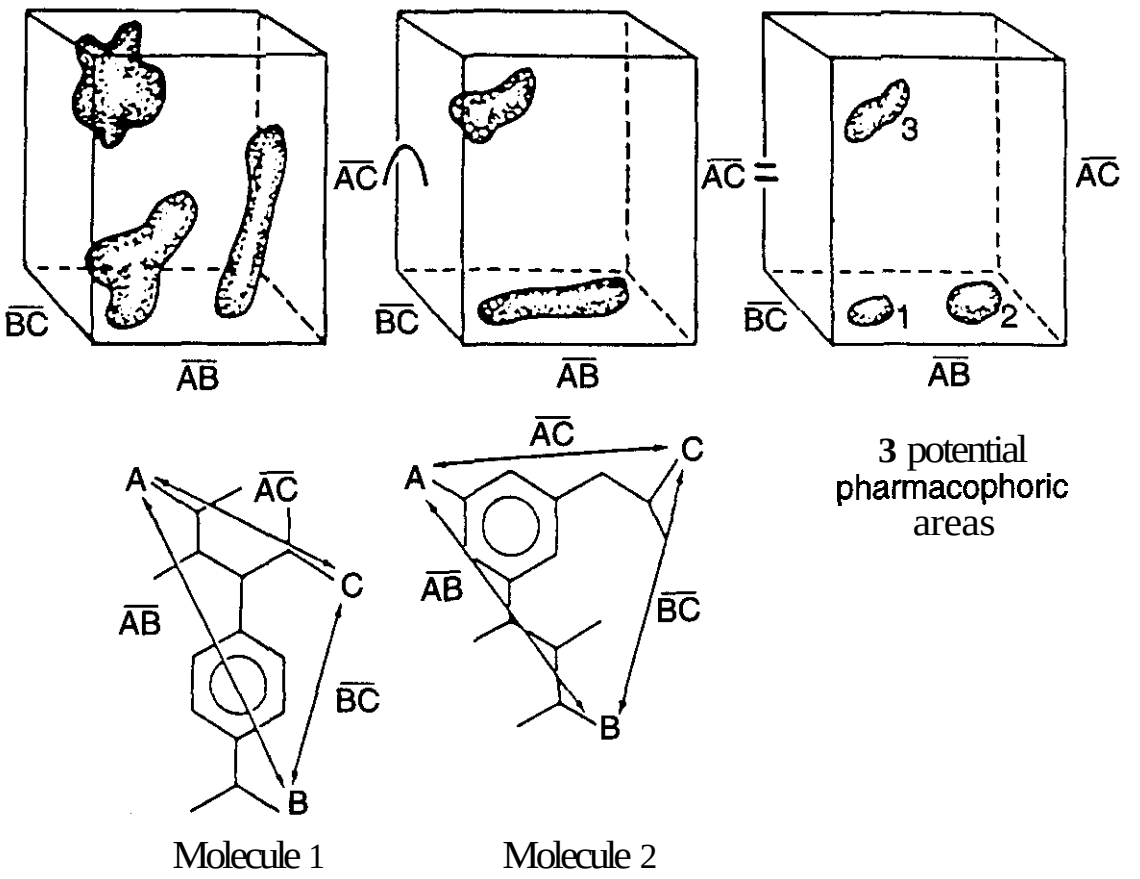

Figure 3.44. OMAPs generated for two molecules can be logically intersected to determine which three-dimensional patterns are common.

provements in algorithms described in the following section have helped to overcome this problem.

4.4.3 Strategic Reductions of Computational Complexity. Logically, the Active Analog Approach can be conceived as sequentially determining all the sterically allowed conformations for each molecule under consideration, generation of an OMAP from those conformations, and logical intersection of the OMAPs to determine the common pharmacophoric patterns. A simple analysis will easily convince one that this is not feasible because of the computational complexity of the problem. For example, the set of 28 ACE inhibitors' (Fig. 3.31), analyzed by Mayer et al. (397), have a total of 163 torsional degrees of freedom that have to be explored to find a common pattern, as seen in Table 3.1. If we were to determine all possible conformations for each molecule at 10° torsional scan, the scan parameter (s) = 10° and the number of torsional increments r = 360°/s, or 36. For each molecule, there are r^n possibilities to be examined. For the set of molecules there are $(6 \times 36^3) + (7 \times 36^5) + (3 \times 36^6) + (5 \times 36^7) + (6 \times 36^8) + (1 \times 36^9)$ possible conformations to be generated and examined. If one compares each conformation of each molecule with all the conformations of the other molecules to find possible correspondences, the combinatorials of the problem explode and one reaches the same level of complexity as a complete conformational search of a peptide of 30 residues at a 10° scan (not currently feasible).

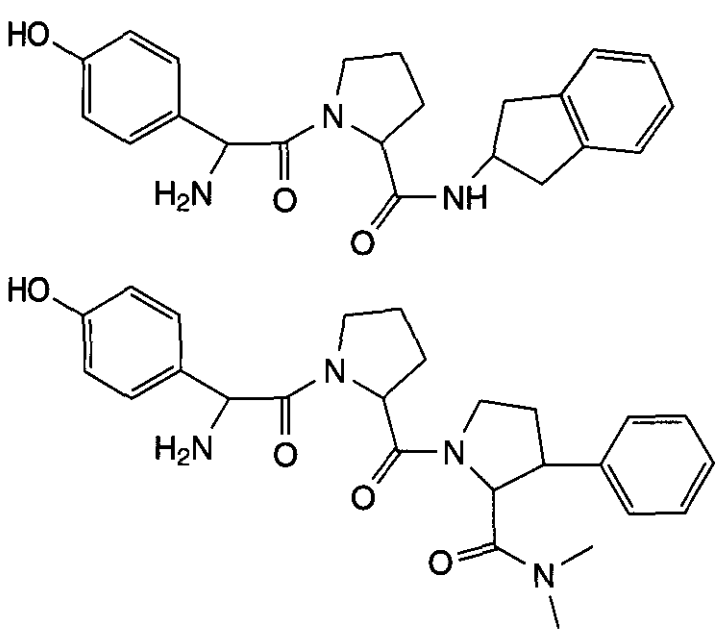

Figure 3.45. Conformations of two constrained analogs of morphiceptin in which aromatic rings of Tyr^1 and Phe^3 are overlapped (445).

One is not interested in the conformational