Primarily associated with sensory neurons and located within specific areas of the central nervous system (CNS), neurokinin-1 (NK-1) is a member of the seven-transmembrane G-protein-coupled receptor family. The tachykinin peptide Substance P is the natural ligand for NK-1 and has been implicated in the pathophysiology of a wide range of diseases including anxiety, asthma, cystitis, emesis, inflammatory bowel disease, migraine, movement disorders, pain, and psoriasis. Merck has identified an octahydro-isoindole-based compound 1 which has significant binding affinity (sub-nanomolar) for the hNK-1 receptor. Compound 1 contains five stereocenters: a central core possessing four contiguous all-trans stereocenters, a pendant bis(trifluoromethyl)benzylic ether, and a cyclopentenone moiety. In order to fully evaluate this compound, an efficient and practical synthesis was required which would allow for the preparation of multi-kilogram quantities to support both preclinical and clinical development. Key to the success of the preparation of 1 was control of the relative and absolute stereochemistry. This presentation will address the evolution of a highly efficient asymmetric synthesis of 1.