Despite the prevalence of the RyR in cardiac function, only a few therapies have been developed for the prevention and treatment of cardiac disease that target the ryanodine receptor (RyR). As part of a broader program aimed at the development of new probes for RyR function, we have initiated a campaign to complete a total synthesis of the natural isoryanoid diterpene perseanol. A highly convergent strategy aimed at efficiently establishing the polycyclic framework of these natural products is detailed. Emphasis will be placed on the strategic use of a fragment coupling approach to overcome the inherent stereochemical bias presented by late-stage intermediates—thereby enabling a 19 step synthesis of the isoryanoid diterpene (+)-perseanol. The development of an efficient and general approach will allow a comprehensive evaluation of these small molecules for the preparation of RyR isoform-selective molecular probes.