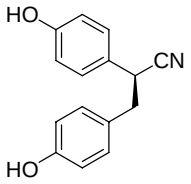
Asymmetric Synthesis of the Estrogen Receptor β Ligand, *S*-2,3-Bis(*p*-hydroxyphenyl)propionitrile (*S*-DPN)

Vincent M. Carroll, Jillian R. Gunther, Kathy Carlson, John A. Katzenellenbogen

Agonists that show a high selectivity for estrogen receptor beta (ERβ) are of interest as probes to study the biology of the two ER subtypes, ERα and ERβ, and for potential therapeutic applications. We have recently described 2,3-bis(*p*-hydroxyphenyl)propionitrile (DPN), which exhibits a 170-fold greater relative potency for ERβ in transcription assays. Unlike other ERβ selective ligands, DPN exists as a racemate, and only recently has it been shown that each enantiomer exhibits different biological effects in the presence of both receptor isoforms. Thus, to further assess the biological activities of each enantiomer on ER, it is necessary to conduct studies using enantiopure material. Described herein is the first reported asymmetric synthesis of both enantiomers of DPN, relying on an Evans asymmetric alkylation to form the stereocenter and subsequent functional group interconversions to generate the desired nitrile in a concise fashion and without racemization.



S-DPN