

ORAL PRESENTATIONS

APPLICATION OF THE “CONTROL FROM ROOT DESIGN” STRATEGY FOR ASYMMETRIC SYNTHESIS OF FINERENONE VIA EVANS’ CHIRAL AUXILIARY

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“Control from Root Design” (CRD) is an organic process R&D strategy that integrates six key criteria: safety, environmental benignity, operational simplicity, health protection, quality assurance, and cost efficiency at the earliest stage of route design. Unlike conventional approaches that optimize sustainability only after route development, CRD embeds synthetic route design and sustainability considerations from project inception [1]. We demonstrate its effectiveness through the redesigned asymmetric synthesis of finerenone.

Despite considerable progress in synthetic methodologies, the efficient construction of the naphthyridine core of finerenone remains a significant challenge. To address this, we designed an asymmetric route to finerenone enabled by a novel one-pot cyclocondensation approach that efficiently furnishes the crucial 4-amino-2-pyridone building block. This key intermediate was constructed via a one-pot cyclocondensation reaction using ammonium acetate as the nitrogen source, enabling the simultaneous formation of two new C–N bonds. The process demonstrates excellent scalability, with production quantities reaching up to 100 g. [2].

Leveraging this intermediate, the stereoselective construction of the naphthyridine core was achieved through cyclization of 4-amino-2-pyridone with a cyanoanisoole bearing Evans’ (R)-4-benzyl-2-oxazolidinone as the chiral auxiliary, delivering the product in 80% yield with a diastereomeric ratio of 86:14. Subsequent alkylation with triethyl orthoacetate under sulfuric acid catalysis, followed by transamidation of the resulting ethyl ester with ammonia, furnished finerenone in 31% overall yield over six linear steps [3]. The resulting route embodies the six CRD criteria in concrete terms: hazardous oxidation and deprotection steps involving nitric acid and hydrogen chloride are eliminated (safety, health protection); ammonium acetate replaces stoichiometric hazardous propionitrile as the nitrogen source (environmental benignity); Evans’ chiral auxiliary supplants precious-metal asymmetric catalysis (cost efficiency); a one-pot reaction telescopes multiple transformations (operational simplicity); and crystallization-based stereochemical upgrade secures the API’s critical quality attributes (quality), all achieved prior to process lock-in.

References:

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3. Abduahadi, S.; Bonku, E. M.; Zhu, F.; Yang, F.; Guma, S. D.; Nuriddinov, Z.; Qin, H.; Shen, J. An Efficient Asymmetric Synthesis of Finerenone via Evans’ Chiral Auxiliary. *Eur. J. Org. Chem.* 2025, 28, e202500538.