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Functional-Group-Tolerant, Nickel-Catalyzed Cross-Coupling Reaction for Enantioselective Construction of Tertiary Methyl-Bearing Stereoisomers

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Synthesis of a Retinoic Acid Receptor Agonist

Scope of the Negishi alkyl–alkyl cross-coupling

Significance: The target molecule **I** is a retinoic acid receptor γ (RAR γ) agonist that is of interest for the treatment of acne, psoriasis and melanoma. The synthesis depicted features the first nickel-catalyzed stereospecific Negishi alkyl–alkyl cross-coupling reaction of secondary benzylic α -(methylthio)acetate esters with dimethylzinc.

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Comment: The mild reaction conditions are compatible with a variety of functional groups including alkenes, protected alkynes, acetals, and esters. Heterocycles, amines, and imides are also well tolerated. Cross-coupling with diethylzinc is also possible but the reaction is more complex owing to additional competitive reaction pathways.

Category

Synthesis of Natural Products and Potential Drugs

Key words

retinoic acid receptor agonist

nickel-catalyzed cross-coupling

α -(methylthio)-acetate esters

dimethylzinc

SYNFACT
of the month