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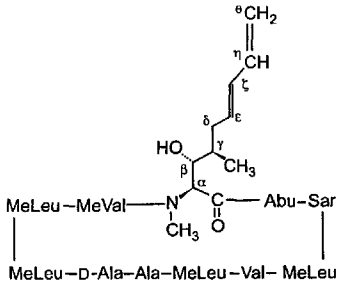
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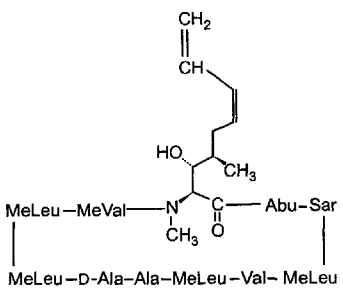
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(54) Title: SYNTHESIS OF CYCLOSPORIN ANALOGS



E-isomer of $ISA_{tx}247$

A



Z-isomer of $ISA_{tx}247$

B

(57) Abstract: The invention is directed to isomeric mixtures of cyclosporine analogues that are structurally similar to cyclosporine A. The mixtures possess enhanced efficacy and reduced toxicity over the individual isomers and over naturally occurring and other presently known cyclosporines and cyclosporine derivatives. Embodiments of the present invention are directed toward *cis* and *trans*-isomers of cyclosporin A analogs referred to as $ISA_{TX}247$, and derivatives thereof. Mixtures of $ISA_{TX}247$ isomers exhibit a combination of enhanced potency and reduced toxicity over the naturally occurring and presently known cyclosporins. $ISA_{TX}247$ isomers and alkylated, arylated, and deuterated derivatives are synthesized by stereoselective pathways where the particular conditions of a reaction determine the degree of stereoselectivity. Stereoselective pathways may utilize a Wittig reaction, or an organometallic reagent comprising inorganic elements such as boron, silicon, titanium, and lithium. The ratio of isomers in a mixture may range from about 10 to 90 percent by weight of the (E)-isomer to about 90 to 10 percent by weight of the (Z)-isomer, based on the total weight of the mixture.

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