Total synthesis towards myriceric acid A and endothelin A receptor antagonistic activity

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Abstract

Our current effort towards the total synthesis of (+)-myriceric acid A, a pentacyclic triterpene isolated from *Myrica cerifera* plant, along with endothelin A receptor antagonistic activity will be presented. Endothelin A receptor antagonists may be used in the relief of vasoconstriction in ischemia, stroke, and hemorrhage in the brain. Utilizing Hagiwara's synthesis of chiral Wieland-Miescher ketone, we constructed a cyclic ketal protected (-)-1,1,4a,8a-tetramethyldodecahydro-2-oxo-phenanthren-8-ol. This key tricyclic sesquiterpene was converted to both tetracyclic diterpene enone through a Michael-aldol condensation reactions and pentacyclic enone via the attachment of an appended side chain followed by a tandem intramolecular Michael-aldol ring closing reaction. The latter reaction is concise and unprecedented. We also discovered a new method for the introduction of hindered quaternary C14α-hydroxymethyl appendage via a stereoselective 1,4-addition reaction of the aforementioned tetracyclic enone with potassium cyanide followed by the formation of cyclic hemi-iminal, and acid-mediated ring opening to give the γ-keto carboxaldehyde. This sequence of transforming reactions of β-cyano ketone to γ-keto carboxaldehyde may be applied to other natural product synthesis. The endothelin antagonistic activities of six synthetic tetracyclic intermediates along with (+)-myriceric acid A were evaluated for their ability in preventing and reversing vasoconstriction caused by endothelin-1 (ET-1), a vasoconstrictive peptide. The EC_{50} values (effective concentrations for 50% inhibition) of vasoconstriction in mouse's spiral modiolar artery caused by ET-1 of the six tetracyclic terpenoids are in the nanomolar ranges.