Studies Towards the Synthesis of Natural Products Ornosol and Insularoside

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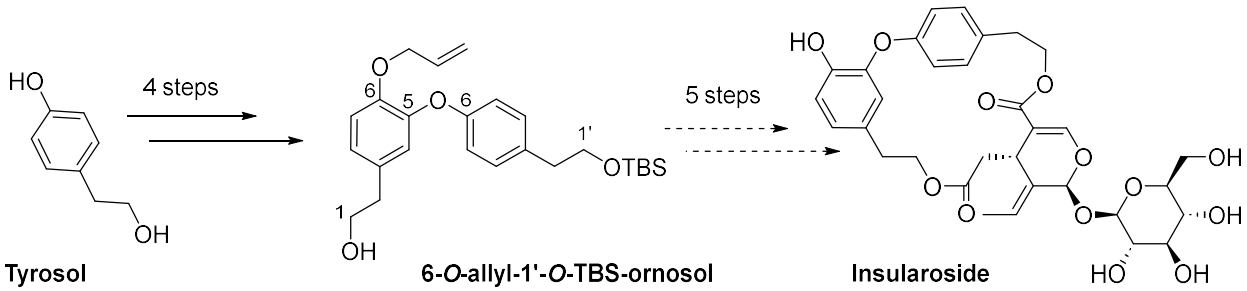
Insularoside and ornosol are bioactive natural products isolated from the *Fraxinus* species.[1] Specifically, insularoside, also known as ornoside, a secoiridoid glucoside from the leaves of *Fraxinus insularis*, was identified as an oleoside-type glucoside containing ornosol, a dimeric tyrosol derivative, isolated from the bark of *Fraxinus ornus*.[1] Naturally occurring ornosol forms a macrocyclic lactone, linked via ester bonds to an oleoside moiety (Scheme).[2] Both natural products are known for their antioxidant and anti-inflammatory properties and contribute to the *Fraxinus* bioactive constituents. Their role in drug discovery is underscored by the significance of natural compounds in developing effective therapeutic agents.[3,4]

We present herein our studies towards the synthesis of ornosol and insularoside, through a regioselective process constituted by three key steps. The commercially available natural product tyrosol (2-(4-hydroxyphenyl)ethanol) was successfully transformed in four steps to a protected derivative of ornosol, via a copper-catalyzed Ullmann reaction.[5] The elaboration of the insularoside skeleton involves a five-step sequence, including a selective esterification between the protected ornosol and the 7-carboxylate of a tetraacetyl derivative of oleoside. Oleoside is derived from oleuropein, itself isolated from olive leaves, in two steps. A key intramolecular macrolactonization reaction together with a series of deprotection reactions have been designed in order obtain the final natural product. The proposed methodology provides a strategic approach for synthesizing other natural products in the secoiridoid family that incorporate the tyrosol moiety.



Scheme 1. Key intermediates in the synthesis of insularoside.

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