Unified and Asymmetric Total Synthesis, Structural Elucidation of Polycyclic Polyprenylated Acylphloroglucinols via Chirality Transfer Strategy

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Abstract:

Introduction: Polycyclic polyprenylated acylphloroglucinols (PPAPs) are an important class of bioactive compounds containing hundreds of natural products. The general asymmetric synthetic strategy towards different types of PPAPs was very limited and only a few PPAPs have been synthesized enantioselectively thus far. Based on the structural and conformational diversity of PPAPs, this thesis aimed to develop a more unified and innovative approach to address the challenge of asymmetric syntheses of multiple types (*endo*/*exo* and A/B types) of PPAPs.

Materials and Methods: Chirality was introduced by CBS reduction or enzyme-catalyzed kinetic resolution, and the chiral center at C7 was constructed by 1,4-chiral induction or chirality transfer strategy via Ireland-Claisen rearrangement. In addition, the bicyclo[3.3.1]nonane-2,4,9-trione skeletons was constructed diastereoselectively by base-catalyzed tandem Dieckmann cyclization. The first asymmetric syntheses of oblongifolin M and its analogs, oblongifolins AA, L and R were accomplished based on diversity-oriented synthesis.

Results: With the key strategy of 1,4-chiral induction or chirality transfer via Ireland-Claisen rearrangement to construct chiral centers at C7, two completely different routes were developed for the asymmetric syntheses of linear precursors with different substituents using a divergent synthesis approach. The base-catalyzed tandem Dieckmann cyclization was developed for the diastereoselective construction of endo/exo-type of bicyclo[3.3.1]nonane-2,4,9-trione skeletons. Using the approach above and based on diversity-oriented synthesis, the first asymmetric syntheses of oblongifolin M and its analogs, oblongifolins AA, L and R, was accomplished, resulting in a structural revision and establishment of the complete configuration.

Conclusions: In summary, we have developed an efficient base-promoted cascade Dieckmann cyclization for the diastereoselective construction of exo- and endo-types of bicyclo[3.3.1]nonane-2,4,9-triones. The reaction was shown to proceed via an 8-membered ring, which could generate both *endo*/*exo* intermediates. There was a remarkable solvent effect-induced diastereodivergence towards *endo*- or *exo*-products, allowing access to complementary diastereomeric pairs with high diastereoselectivity from the same starting materials. The asymmetric total synthesis features a chirality transfer strategy via a CBS reduction/SN2 reaction/oxidation or enzyme-catalyzed kinetic resolution/Ireland–Claisen rearrangement, and following reactions to achieve a general method to the enantioenriched PPAPs. The first asymmetric total syntheses of both enantiomers of oblongifolin M, oblongifolin L, oblongifolin R and oblongifolin AA via a linear 11–13 steps in one sequence were achieved. The diversity-oriented synthesis strategy also allows a series of structural revision and establishment of the complete configuration.

References:

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