The Total Syntheses of Lorneic Acids A, F, and J

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• Abstract:

An alternative faster synthesis to lorneic acid A and the first total syntheses of lorniec acids F and J are described. Lorneic acid A, F and J are both constructed in 4 steps from 2-bromo-5-metylbenzaldehyde in overall yields of 30%, 45%, and 24% respectively.

• Introduction:

Actinomycetes, are a type of bacteria that is found in the roots of plants, and produce secondary metabolites that have the potential of being bioactive compounds. Examples include lorneic acids (A-K) (**Figure 1**).[1,2] In 2009, lorneic acids A and B were extracted from an actinomyces strain, *Streptomyces* (NPS554) and found to possess significant inhibitory activity against phosphodiesterase 5.[3] As phosphodiesterase inhibitors, these lorneic acids can be potential therapeutics for arterial hypertension, dementia, depression, and schizophrenia. Recently, 7 new lorneic acids (C-K) were extracted from an endophytic acitonomycete strain, *Streptomyces* (KIB-H1289), isolated from the Nakai plant found in China. The plant, in traditional Chinese medicine, has been used for the treatment of pneumonia and bronchitis. The firsts and only total syntheses of lorneic acids A and B were accomplished from 4-methylbenzoic acid, in 11-12 steps with overall yields of 20-26%.[3] Presently, there are no reported syntheses of lorneic acids C-K and no biological investigations have been pursued.

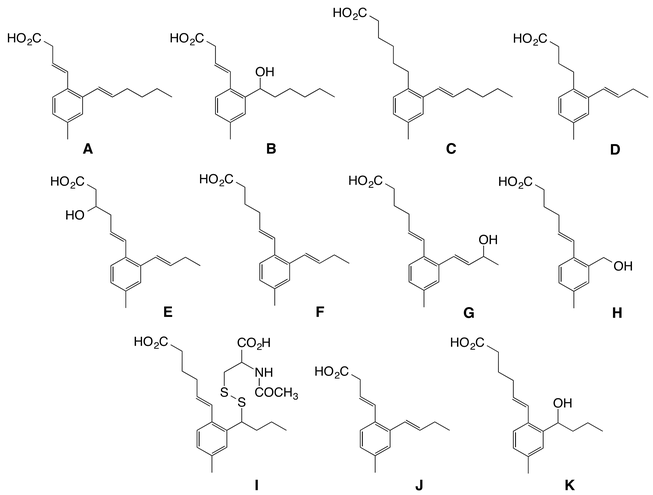
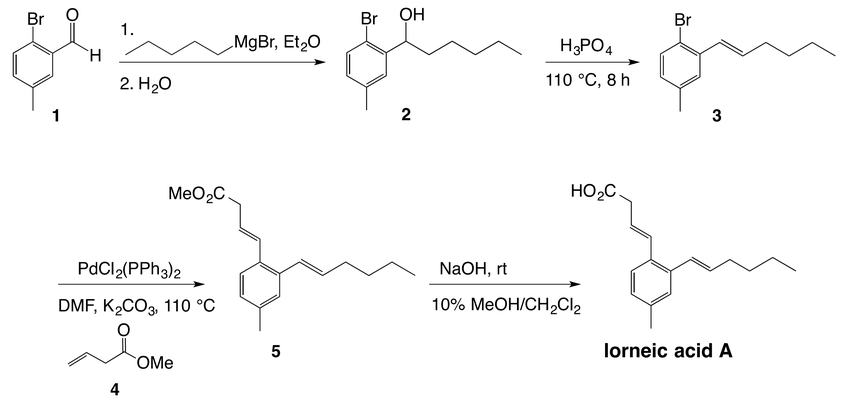


Figure 1. Lorneic Acids A-K

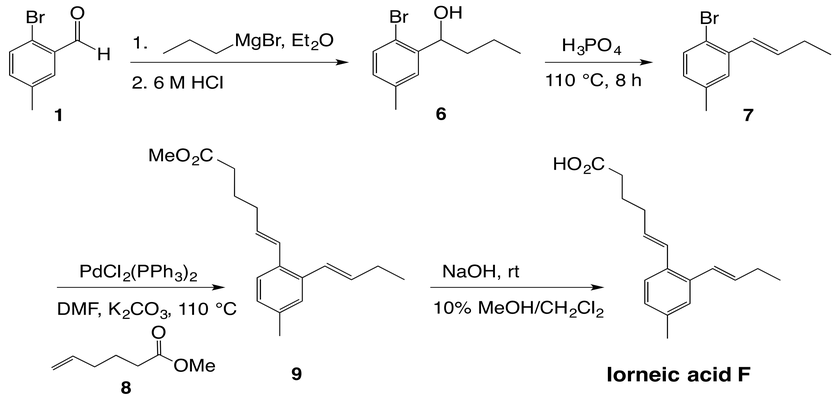
Herein we report expeditious routes towards lorneic acids F and J. In addition, we report an alternative route toward the construction of lorneic acid A in four steps as opposed to 11 steps.

• Total Synthesis of Lorneic Acid A:



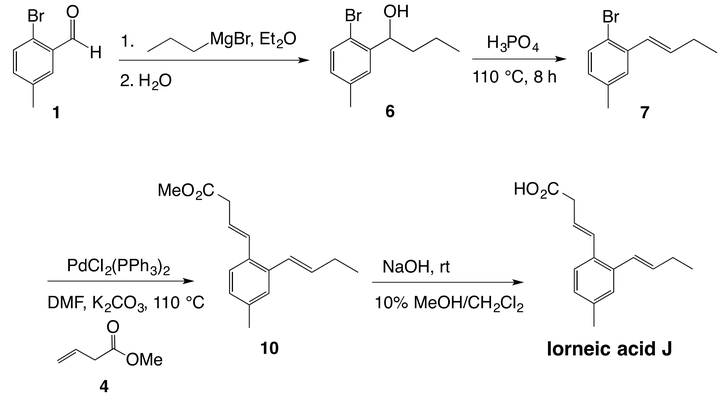
The total synthesis of lorneic acid A was initiated with the Grignard addition of pentylmagneisum bromide to aryl bromide **1** to yield the secondary benzylic alcohol **2** in 86% yield. Dehydration under acidic conditions yielded the desired *trans* olefin in 85%. A Heck reaction between the aryl bromide (**3**) and methyl 3-butenoate (**4**) provided the second side arm to the molecule in 51% yield. Finally, hydrolysis of the ester to the carboxylic acid accomplished the construction of the natural product in 81% yield.

• Total Synthesis of Lorneic Acid F:



The synthesis of lorneic acid F was shown to proceed in four steps from aryl bromide **1**. The formation of benzyl alcohol **6** proceeded via the Grignard addition of propyl magnesium bromide to 2-bromo-5-methylbenzaldehyde **1**, followed by treatment of the alcohol with phosphoric acid to yield the desired *trans*-olefin (**7**) as the only isomer. The key step to the synthesis included a palladium catalyzed Heck reaction of aryl bromide **7** with methyl 5-hexenoate (**8**), in the presence of triphenyl posphine and triethyl amine.[5] The cross-coupling reaction afforded alkene **9**, with *trans*-selectivity, in 73% yield. Finally, hydrolysis of the ester with sodiium hydroxide in 10% methanol/dichloromethane at 100 °C resulted in the desired target, lorneic acid **F**, in 85% yield. The resulting natural product was completed in four steps from 2-bromo-5-methylbenzaldehyde (**1**) with an overall yield of 45%.

• Total Synthesis of Lorneic Acid J:



- The total synthesis of lorneic acid J was accomplished in a similar manner to that of lorneic acid A and F. This synthetic route used the same aryl bromide intermediate used for lorneic acid F, however, the cross coupling in this case was with methyl 3-butenoate (**4**), in the presence of triphenyl posphine and potassium carbonate. This reaction afforded alkene **9**, with *trans*-selectivity, in 43% yield. Hydrolysis of the ester with sodium hydroxide in 10% methanol/dichloromethane at 100 °C resulted in the desired target, lorneic acid **F**, in 77% yield. The resulting natural product was completed in four steps from 2-bromo-5-methylbenzaldehyde (**1**) with an overall yield of 24%.

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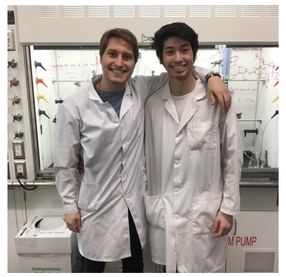

• References:

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