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Synthetic Pathway of (3S,7S,8S)-3-((E)-3,4-dihydroxypent-1-en-1-yl)-7,8-dihydroxy-7-methyl-3,4,7,8-tetrahydro-6H-isochromen-6-one

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Abstract

Retrosynthetic analysis was the fundamental and most useful method in determining a synthesis pathway for a compound in organic chemistry. It guided the chemists to observe the connectivity of a molecule, chose a way of disassembling the large molecule into smaller (simpler) ones, and finally figured out the synthesis of those disassembled pieces. We have utilized such method in designing our own synthetic pathway of (3S,7S,8S) -3 -((E) -3, 4 -dihydroxypent-1-en-1-yl) -7, 8 -dihydroxy -7 -methyl -3,4,7,8-tetrahydro-6H-isochromen-6-one. We chose 3-methylcyclohex-2-en-1-one and (R)-3-bromo-2-hydroxypropanal as starting molecules for our pathway. Figure 1 shows the structure of 3-methylcyclohex-2-3n-1-one and Figure 2 shows the structure of (R)-3-bromo-2-hydroxypropanal.

Keywords

Retrosynthetic Analysis; Possible Synthetic Pathway; Potential Advantages and Disadvantages.

1. Introduction and Background

(3S,7S,8S)-3-((E)-3, 4-dihydroxypent-1-en-1-yl)-7, 8-dihydroxy-7-methyl-3, 4, 7, 8-tetrahydro-6H-isochromen-6-one is one of the compounds isolated from the coculture of phytopathogen-phytopathogen. This was a totally new compound and there is no confirmed synthesis pathway given out until now. According to the research done on the biological combinations of Metabolite Productions and the structural elucidation, the specific structure of the compound was determined by comparing its CD spectrum with the following compound which was named as nigcollin B[1].

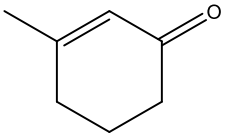

Figure 1. The structure of 3-methylcyclohex-2-en-1-one

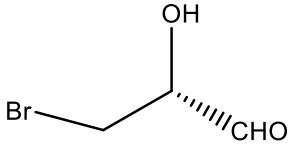

Figure 2. The structure of (R)-3-bromo-2-hydroxypropanal

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Figure 1 shows the structure of 3-methylcyclohex-2-3n-1-one and Figure 2 shows the structure of (R)-3-bromo-2-hydroxypropanal.

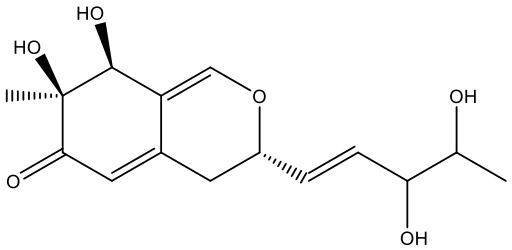

Figure 3. The structure of (3S,7S,8S)-3-((E)-3,4-dihydroxypent-1-en-1-yl)-7,8-dihydroxy-7-methyl-3,4,7,8-tetrahydro-6H-isochromen-6-one

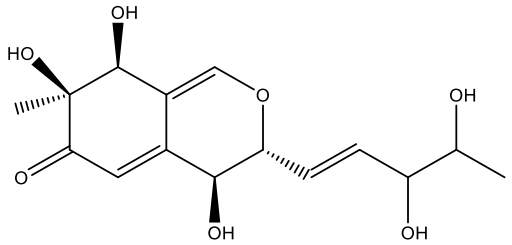

Figure 4. The structure of nigcollin B

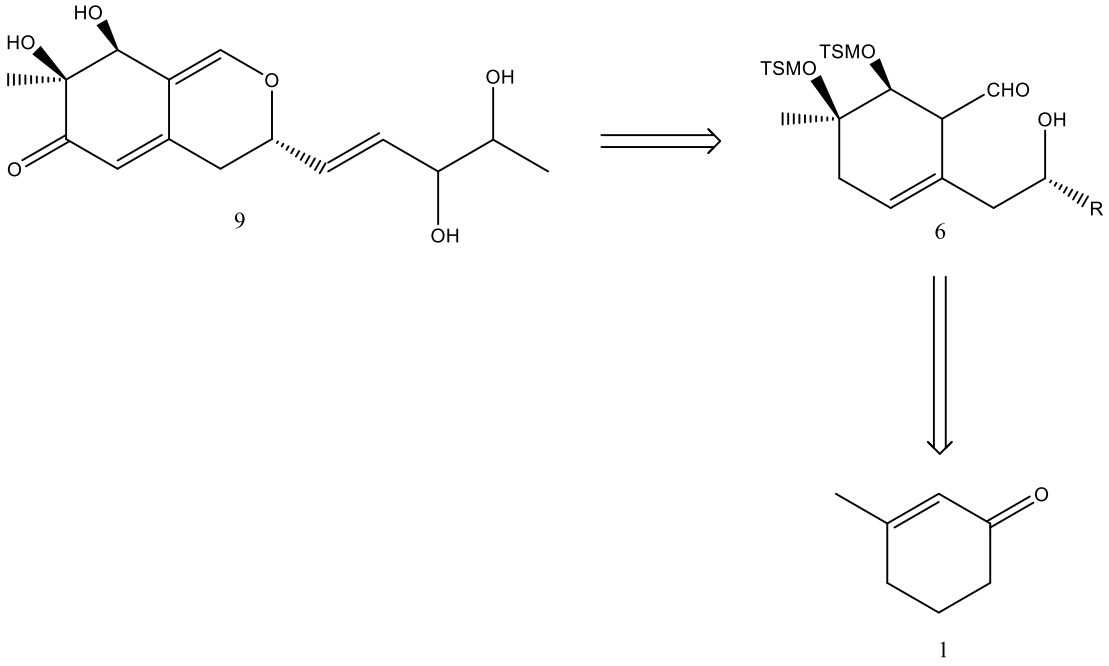

Figure 5. Retrosynthetic pathway to 3-methylcyclohex-2-en-1-one

Figure 3 is the structure of the new found compound which was named as (3S,7S,8S)-3-((E)-3,4-dihydroxypent-1-en-1-yl)-7,8-dihydroxy-7-methyl-3,4,7,8-tetrahydro-6H-isochromen-6-one. Figure 4 is the structure of nigcollin B, which is used as a comparative compound regarding to (3S,7S,8S)-3-((E)-3,4-dihydroxypent-1-en-1-yl)-7,8-dihydroxy-7-methyl-3,4,7,8-tetrahydro-6H-isochromen-6-one. Figure 5 is the basic retrosynthesis route considered to develop the final synthesis of the product.

2. Synthesis Analysis

Synthetic Pathway of (3S,7S,8S)-3-((E)-3,4-dihydroxypent-1-en-1-yl)-7,8-dihydroxy-7-methyl-3,4,7,8-tetrahydro-6H-isochromen-6-one

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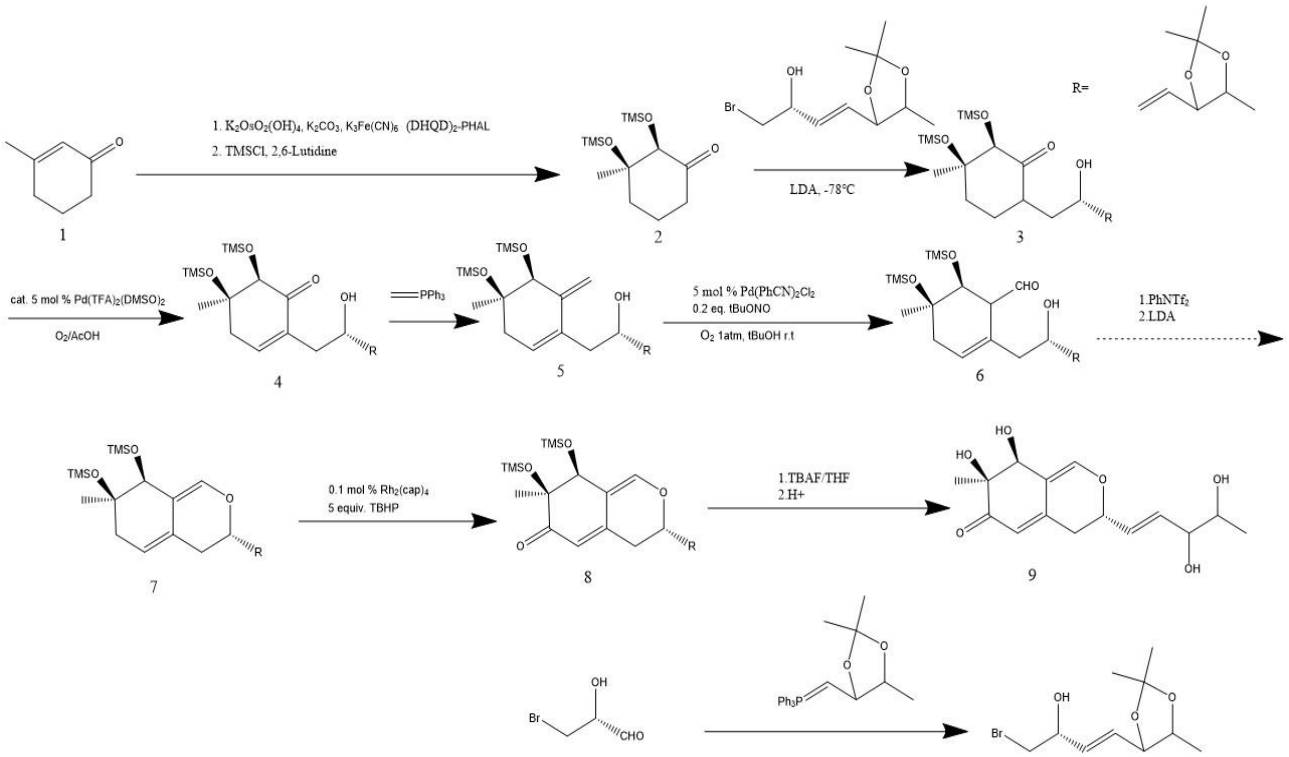

Figure 6. Synthetic Pathway of (3S,7S,8S)-3-((E)-3,4-dihydroxypent-1-en-1-yl)-7,8-dihydroxy-7-methyl-3,4,7,8-tetrahydro-6H-isochromen-6-one

The starting point of the retrosynthesis was breaking one bond of the ether in the compound since it is able to create ether by arising the reaction between aldehyde and alcohol by using $PhNTf_2$and LDA. It was an unconfirmed step, and we proposed that converting the alcohol to triflate, which would let it to leave easier, and therefore condense with the enol generated with LDA. LDA was also a bulky base so Li-X exchange would not occur. (This step is not confirmed, and we are wondering whether we can form ester in the previous step and use Et_3SiH in the presence of a catalytic amount of $InBr_3$ to produce the corresponding ether in the molecule[2].

Since now aldehyde and alcohol existed in the molecule, according to further retrosynthetic analysis, the synthetic equivalent would be compound 5. The forward reaction from compound 5 to 6 could pursue regioselective Wacker–Tsuji oxidation. The yield of the reaction is about 51% according to the research results of different forms of Wacker–Tsuji oxidation which is able to continue the following step. Furthermore, regioselectivity can be solved mostly by using this reaction since the selectivity rate is roughly about 5:1. Even though it was hard to get completely pure substances, we can still continue the following step[3].

The forward reaction from compound 4 to compound 5 was Wittig reaction here, which converted ketone in the molecule to alkene. The Wittig reagent did not influence the other functional groups in the molecule such alcohol group and it probably did not impact TMSO attached on the ring. Additionally, ketone in the molecule was not too sterically hindered so it wouldn't lower the reaction rate and yield a lot.

The forward reaction from compound 3 to 4 was an dehydrogenation reaction, in which $Pd(TFA)_2(DMSO)_2$ was used as a catalyst. In comparison with halogen/chalcogen oxidization and elimination process, this approach was much more facile and cleaner. It also gave out a higher yield[4].

The side chain could be easily produced and added to the ring, by a classical Wittig reaction and alkylation with LDA. At last, the two hydroxyls could be added by the Sharpless asymmetric dihydroxylation.

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Inconclusion, the synthesis pathway is mostly able to synthesize the target molecule (3S,7S,8S)-3-((E)-3,4-dihydroxypent-1-en-1-yl)-7,8-dihydroxy-7-methyl-3,4,7,8-tetrahydro-6H-isochromen-6-one in 9 steps with minimum hindrance from reaction yield or regioselectivity (to our knowledge) compare to other possible pathway designed by us.

3. Conclusion

In conclusion, the synthesis pathway is mostly able to synthesize the target molecule (3S,7S,8S)-3-((E)-3,4-dihydroxypent-1-en-1-yl)-7,8-dihydroxy-7-methyl-3,4,7,8-tetrahydro-6H-isochromen-6-one in 9 steps with minimum hindrance from reaction yield or regioselectivity (to our knowledge) compare to other possible pathway designed by us.

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