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合成白藜芦醇糖苷的研究进展

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摘 要

白藜芦醇糖苷是一种分布在自然界中的二苯乙烯类天然产物。白藜芦醇糖苷具有很高的药用价值，如镇咳、平喘、降血脂等多种药理作用。它的药理作用和白藜芦醇相近，其药用价值相对白藜芦醇有明显的提升。研究表明，糖苷化的白藜芦醇在药理上有较好的生物利用度和靶向性，因其独特的优势引起了众多化学与生物研究者的关注。本文收集了白藜芦醇糖苷的研究进展，包括生物酶合成法和化学合成法并进行了讨论，希望能为进一步研究开发利用白藜芦醇糖苷提供一定的参考。

关键词

白藜芦醇，糖苷，糖苷化，白藜芦醇糖苷

Research Progress in the Synthesis of Resveratrol Glycosides

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Abstract

Resveratrol glycoside is a stilbene natural product distributed in nature. Resveratrol glycosides have high medicinal value, such as anti-tussive, anti-asthmatic, hypolipidemic and other pharmacological effects. Its pharmacological action is similar to that of resveratrol, and its medicinal value is significantly improved compared with resveratrol. Studies have shown that glycosidic resveratrol has good bioavailability and targeting in pharmacology, which has attracted the attention of many chemical and biological researchers because of its unique advantages. This paper collects and discusses the research progress of resveratrol glycosides, including biological enzymatic synthesis and chemical synthesis, hoping to provide some reference for further research, develop-

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ment and utilization of resveratrol glycosides.

Keywords

Resveratrol, Glycosides, Glycosidation, Resveratrol Glycoside

1. 引言

白藜芦醇 1 (图 1) [1]，是一种天然多酚类的化合物。其于 1924 被发现，1940 年被日本学者 Takaok 首次从毛叶藜芦的根茎中分离出来。白藜芦醇在自然界中分布广泛，主要分布于廖属、葡萄属、藜芦属等植物中，到目前为止，至少已在 34 科、69 属的 100 种植物中被发现[2]。其因具有多种生物活性[3]和较好的药用价值[4]，如抗癌[5]、抗肿瘤[6]、抗糖尿病[7]、抗氧化[8]、神经保护和心血管保护[9]等功效，而备受关注。

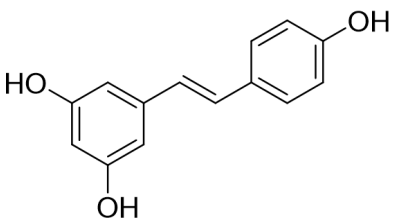

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Figure 1. Structure of resveratrol
图 1. 白藜芦醇的结构

糖苷广泛存在于生物体内，也是糖存在于自然界中的一种形式。糖苷一般是指单糖的半缩醛羟基和醇或者酚的羟基发生反应，失水从而形成的缩醛式衍生物[10]，由糖基受体和糖基给体两部分组成。也可以理解为糖苷是由糖或糖的衍生物等与另一个非糖物质通过其端基碳原子联接而成的化合物。具有生物活性的物质与糖反应生成糖苷，会使其毒性降低、水溶性提高。糖苷的分类也是多种多样的，根据苷元的结构不同可以分为香豆素苷、蒽醌苷、吲哚苷、黄酮苷等；根据糖苷在生物体内的存在形式可分为原生苷、次级苷；根据苷键原子的不同可分为氧糖苷、碳糖苷、硫糖苷、氮糖苷等[11]。氧糖苷类化合物在提高免疫力、抗病毒、抗肿瘤等方面存在着良好的药理活性[12]。经文献报道的糖苷化学合成方法有：糖基卤化物法[13]、硫糖苷法[14]、三氯乙酰亚胺酯法[15]、1-O-硅烷醚糖法[16]、1-O-酰基糖供体法[17]、卤代乙酸酯法[18]、原酸酯法[19]、相转移催化法[20]、烯糖法[21]等。

白藜芦醇糖苷属于天然多酚类化合物，是白藜芦醇和葡萄糖结合的产物。最初是在中药虎杖中被发现的，它与白藜芦醇具有相似的药理活性[22]。白藜芦醇的水溶性很差而且还容易发生氧化[23]。在白藜芦醇单体上引入糖基供体后其稳定性[24]、水溶性、抗氧化性和生物活性都有所提升。因为白藜芦醇糖苷复杂多样的生物活性，使其在医药[25]、化妆等领域拥有广阔的应用前景[26]。

近些年，研究发现白藜芦醇苷类化合物具有脑组织的保护、抗炎、抗衰老、抗肿瘤、降血脂、心血

管活性和免疫调节等药理活性，因此其具有很高的药用价值，已引起人们广泛的关注。本文收集了白藜芦醇糖苷的研究进展，其中包括生物酶合成法和化学合成法并进行了讨论，希望能为进一步研究开发利用白藜芦醇糖苷提供一定的参考。

2. 白藜芦醇糖苷的研究进展

目前，获得白藜芦醇糖苷的方法有植物提取法[27] [28] [29] [30] [31]和合成法[32]两种，合成法又分为化学合成法和生物酶合成法[33]。从植物中提取的方法是获得白藜芦醇苷的主要途径，但该方法产量较低无法满足市场需求。生物酶合成法是以酶作为催化剂，糖作为糖基供体，白藜芦醇为受体进行反应得到白藜芦醇糖苷[34]。化学合成的方法首先需要对糖基供体进行活化，对糖基受体进行适当的保护，最后糖基供体与糖基受体发生反应得到目标产物[35]。因为白藜芦醇糖苷较高的药用价值[36]，研究者们一直都在探索如何合成白藜芦醇糖苷，但到目前为止合成的白藜芦醇糖苷还是以氧糖苷为主，碳糖苷的合成未见报道。

2.1. 白藜芦醇糖苷的生物酶合成

2014 年 Hiroki Hamada 团队将枯草芽孢杆菌作为葡萄糖基转移酶(PaGT3 酶)的来源(图 2) [37]。用 PaGT3 酶对白藜芦醇、紫檀芪[38]、白皮杉醇[39]进行了糖苷化的探索并对产物的药理活性进行了讨论。其中 PaGT3 酶将白藜芦醇糖苷化为白藜芦醇 3-β-葡萄糖苷和 4'-β-葡萄糖苷、PaGT3 酶将紫檀芪糖苷化为其 4'-β-葡萄糖苷、PaGT3 酶将白皮杉醇糖苷化为其 4'-β-葡萄糖苷。

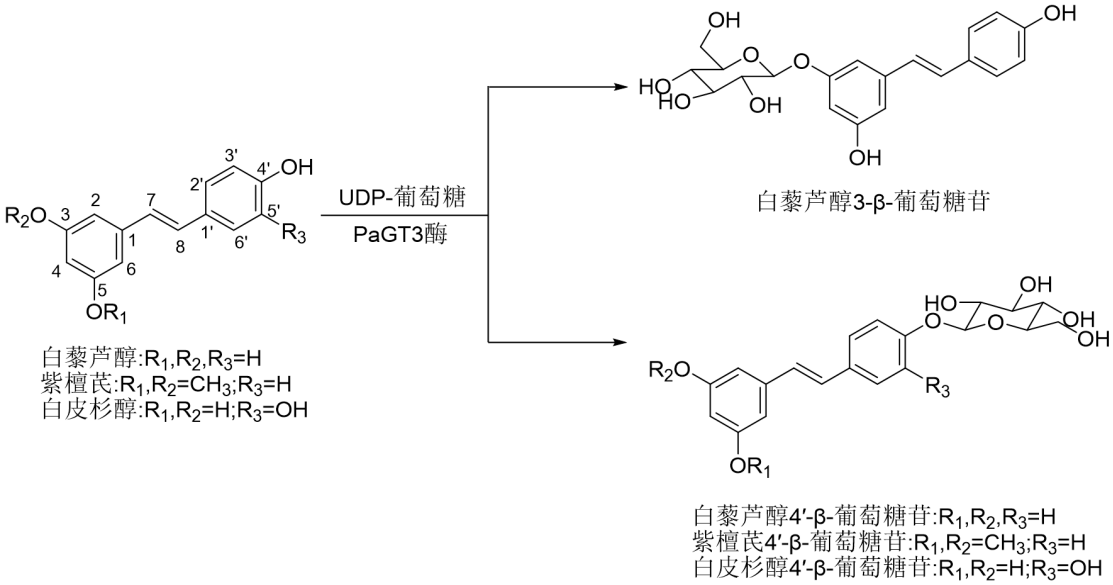


Figure 2. Hiroki Hamada's route for synthesis of resveratrol glycosides
图 2. Hiroki Hamada 团队合成白藜芦醇糖苷路线

2014 年 Ramesh Prasad Pandey 团队从地衣芽孢杆菌[40]中筛选获得了糖基转移酶 YjiC (图 3) [41]。以 UDP-D-葡萄糖为供糖体，在 YjiC 酶催化下白藜芦醇与 UDP-D-葡萄糖反应，可产生四种白藜芦醇苷。分别为白藜芦醇 3-O-β-D-葡萄糖苷、白藜芦醇 4'-O-β-D-葡萄糖苷、白藜芦醇 3,5-O-β-D-二葡萄糖苷和白藜芦醇 3,5,4'-O-β-D-三葡萄糖苷，该过程中白藜芦醇的生物转化率有显著提高(90%)。并通过实践研究发现糖基转移酶 YjiC 具有生产结构多样的白藜芦醇苷的能力。

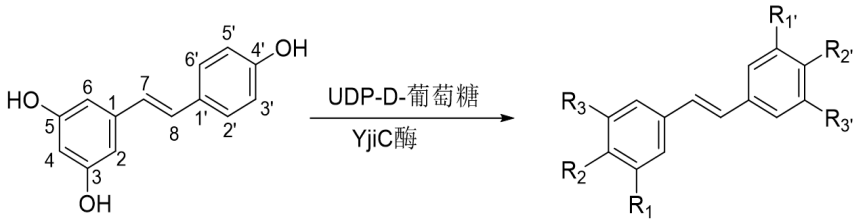


Figure 3. Ramesh Prasad Pandey's route for synthesis of resveratrol glycosides
图 3. Ramesh Prasad Pandey 团队合成白藜芦醇糖苷路线

2020 年王书元团队对于淀粉蔗糖酶[42]催化白藜芦醇的性质进行了探索(图 4) [43]。将中度嗜热菌 Deinococcusgeothermalis 作为淀粉蔗糖酶 DGAS 的来源，以蔗糖为葡萄糖基的供体，白藜芦醇为受体进行生物酶合成反应。淀粉蔗糖酶 DGAS 对白藜芦醇产生催化作用，合成了两个白藜芦醇糖苷，分别为白藜芦醇-4'-O-α-D-吡喃葡萄糖苷和白藜芦醇-4'-O-α-D-吡喃葡萄糖基-(1→4)-O-α-D-吡喃葡萄糖苷。

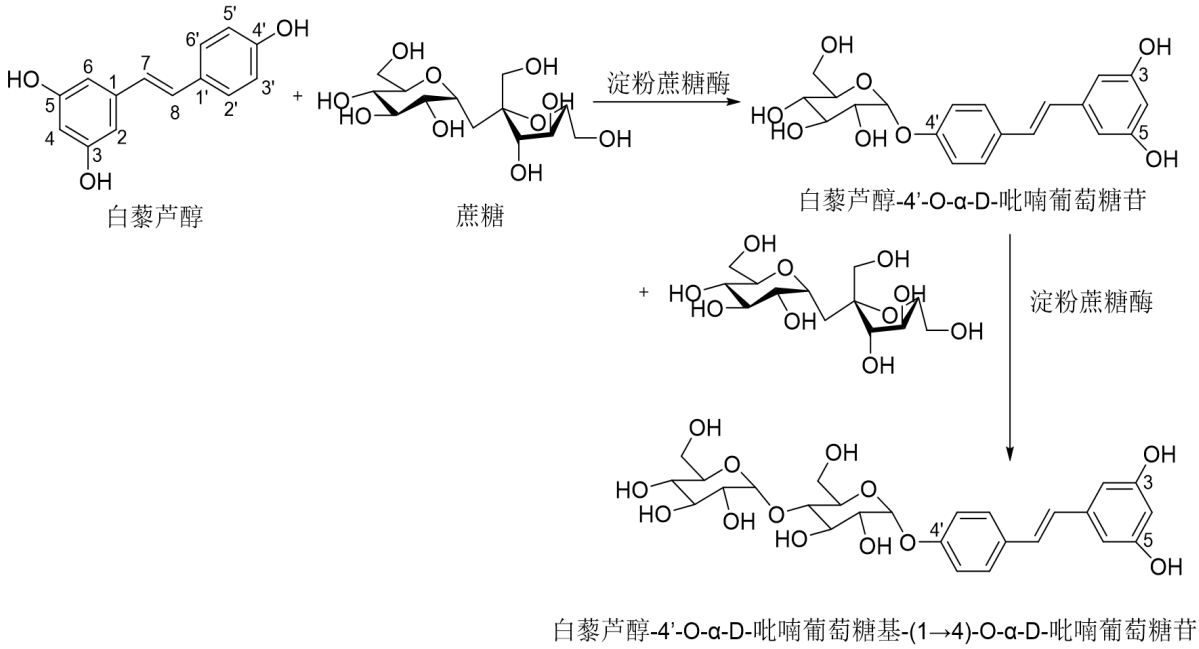


Figure 4. Wang Shuyuan's route for synthesis of resveratrol glycosides
图 4. 王书元团队合成白藜芦醇糖苷路线

2.2. 白藜芦醇糖苷的化学合成

1997 年 FulviaOrsini 团队用化学方法合成了白藜芦醇糖苷(图 5) [44]。先通过 wittig 反应[45]建立双键再脱除硅醚基的保护得到 4'位被甲基保护的顺式和反式白藜芦醇单体(2-5、2-6)。之后以乙酰溴 α-D-葡萄糖作为糖基供体，被保护的反式白藜芦醇单体为受体进行糖苷化反应得到了反式的白藜芦醇糖苷类似物 2-7。最后先脱除糖上的乙酰基保护再脱除单体上的甲基保护得到目标产物白藜芦醇 3-β-D-葡萄糖苷。

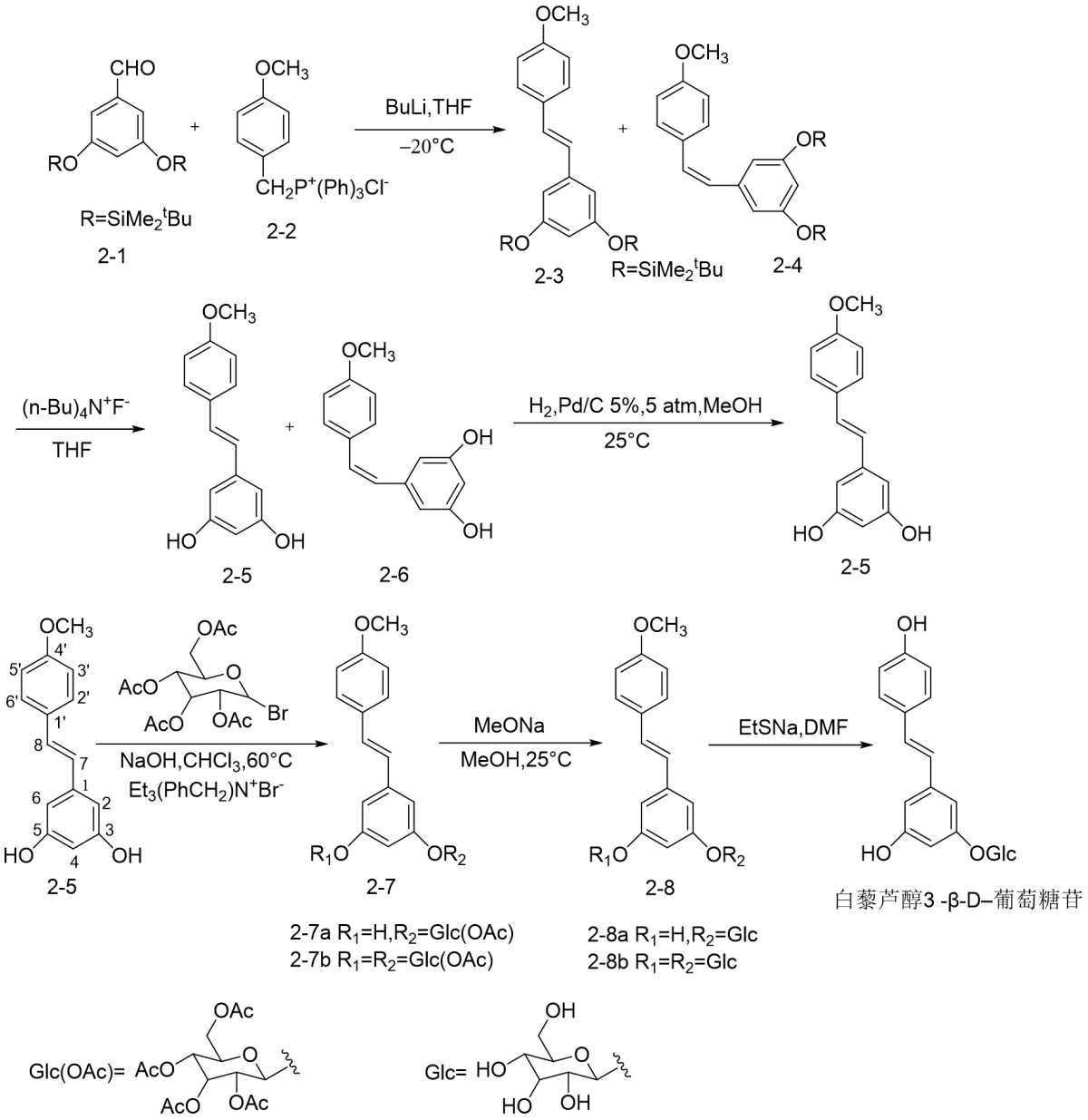


Figure 5. FulviaOrsini's route for synthesis of resveratrol glycosides
图 5. FulviaOrsini 团队合成白藜芦醇糖苷路线

2003 年 G Regev-Shoshani 团队用简单的一步法合成了两种白藜芦醇糖苷(图 6) [46]。采用 Koenigs-Knorr 方法[47] [48] [49]对糖苷化反应进行了一些改进，以白藜芦醇单体为受体，乙酰溴 α-D-葡萄糖为糖基供体，在强碱的催化下直接发生糖苷化反应，最后用高效液相色谱法对糖苷化反应的产物进行分离纯化。得到反式白藜芦醇 4'-O-β-D-葡萄糖苷(产率 12%)和反式白藜芦醇 3-O-β-D-葡萄糖苷(产率 10%)，此方法合成路线最为简单。

2010 年任金红团队应用保护基策略,采用 Schmidt 成苷法[50] [51] [52]制得了 10 个白藜芦醇的单糖苷化衍生物(图 7) [53]。首先利用叔丁基二甲基氯硅烷(TBS)对白藜芦醇上的酚羟基进行随机保护，得到了 5 个白藜芦醇类似物(TBS-Res、TBS-Res-4'-OH、TBS-Res-3-OH、TBS-Res-3,4'-OH、TBS-Res-3,5-OH)。再

将只剩一个羟基未保护的化合物(TBS-Res-4'-OH、TBS-Res-3-OH)分别与各种天然单糖的三氯乙酰亚胺酯经 Schmidt 成苷法进行糖苷化反应。最后对其进行脱保护反应，将之前的硅醚和苯甲酰保护基脱除，再经过 RP-HPLC 纯化得到了 10 个白藜芦醇单糖苷衍生物，并且对其的药理活性进行了分析讨论。

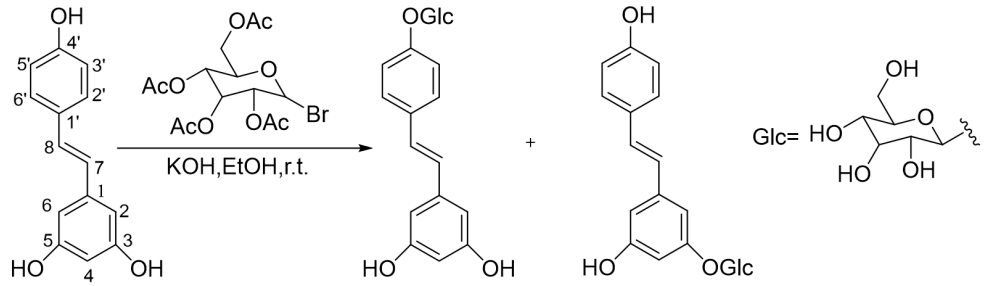
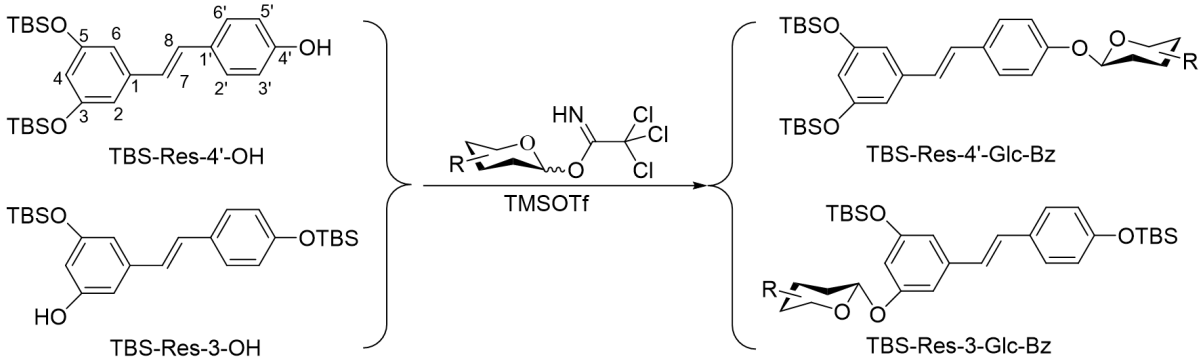


Figure 6.G Regev-Shoshani's route for synthesis of resveratrol glycosides
图 6. G Regev-Shoshani 团队合成白藜芦醇糖苷路线



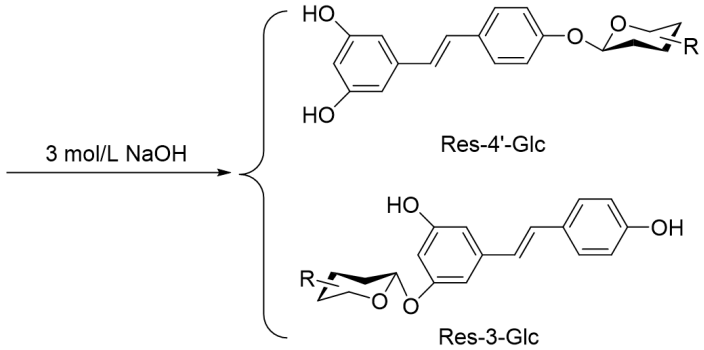


Figure 7. Ren Jinhong's route for synthesis of resveratrol glycosides
图 7. 任金红团队合成白藜芦醇糖苷路线

3. 总结

已有研究表明，白藜芦醇的葡萄糖苷类似物比母体化合物白藜芦醇有更好的生物活性，更高的水溶性和生物利用度，因其优越的药理活性，使得许多学者对它的合成方法产生了浓厚的兴趣。以上总结了近些年来部分白藜芦醇糖苷的合成方法，有生物酶合成法和化学合成法。化学合成法产率低、过程繁琐，

生物酶合成法相对于化学合成法而言产率有所提升，但这两种合成方法都只停留在白藜芦醇氧糖苷的合成阶段，白藜芦醇碳糖苷依旧需要从植物中分离得到。因此，寻找一种高效、简便、经济、绿色、环保的合成白藜芦醇糖苷的方法仍然具有挑战性，目前已成为了一个潜在的研究热点。

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