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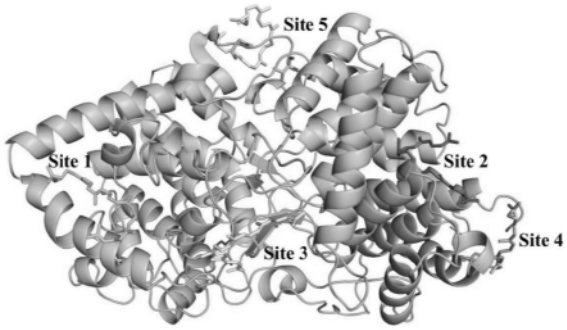
(54)发明名称

一种香树脂醇合酶突变体及其应用

(57)摘要

本发明涉及一种定点突变改造的香树脂醇合酶突变体及其应用,属于酶工程技术领域。所述突变体是将SEQ ID NO.1所示氨基酸序列第323位的亮氨酸替换为丙氨酸;或第328位的亮氨酸替换为丙氨酸;或第331位的苯丙氨酸替换为丙氨酸;或第341位的半胱氨酸替换为丙氨酸。本发明构建的香树脂醇合酶突变体通过在解脂耶氏酵母中表达,与出发菌株即未突变菌株相比α-香树脂醇和β-香树脂醇的产量均有所提升,其中α-香树脂醇的产量最多提升12.38倍,β-香树脂醇的产量最多提产7.99倍。改造后的基因工程菌株,更适合工业应用,可降低生产成本,提高生产效率。



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1.一种香树脂醇合酶突变体,其特征在于,所述的香树脂醇合酶突变体,是在SEQ ID NO.1所示的野生型香树脂醇合酶基础上,将第323位的亮氨酸替换为丙氨酸所得。

2.如权利要求1所述的香树脂醇合酶突变体,其特征在于,所述突变体氨基酸序列如SEQ ID NO.2所示。

3.权利要求1所述的香树脂醇合酶突变体的编码基因。

4.如权利要求3所述的编码基因,其特征在于,核苷酸序列如SEQ ID NO.7所示。

5.含有权利要求3所述编码基因的重组载体或重组菌株。

6.如权利要求5所述的重组载体,其特征在于,采用的表达质粒为pYLEX1或pUG6。

7.如权利要求5所述的重组菌株,其特征在于,采用的宿主细胞为解脂耶氏酵母、酿酒酵母、乳酸克鲁维酵母或大肠杆菌。

8.如权利要求5所述的重组菌株,其特征在于,所述重组菌以解脂耶氏酵母Po1gΔKU70为宿主,采用pYLEX1质粒对SEQ ID NO.7所示基因进行表达。

9.权利要求5所述重组载体或重组菌株在生产香树脂醇中的应用。

10.权利要求1所述香树脂醇合酶突变体在生产香树脂醇中的应用。

一种香树脂醇合酶突变体及其应用

技术领域：

[0001] 本发明涉及一种定点突变改造的香树脂醇合酶突变体及其应用，属于酶工程技术领域。

背景技术：

[0002] 香树脂醇($C_{30}H_{50}O$)是一类五环三萜化合物，是植物中丰富的次生代谢产物之一。在自然界中，香树脂醇是以游离或成酯形式存在于植物中的，并有α-香树脂醇和β-香树脂醇两种同分异构体。他们具有广泛的药理活性以及药用价值，包括抗炎、抗菌、抗癌、保护肝脏、提高免疫力等，市场应用价值极高。

[0003] 本发明的香树脂醇合酶(CrMAS)基因从长春花中获取，通过分子模拟和分子对接预测其有五个关键结合口袋，选择结合力最高的口袋进行后续研究。香树脂醇合酶可以和底物2,3-氧化角鲨烯通过疏水作用结合并同时产生α-香树脂醇和β-香树脂醇。

[0004] 定点突变是指通过聚合酶链式反应(PCR)的方法向目的DNA片段(质粒或基因组)中引入所需变化，包括碱基的添加、删除、点突变等。定点突变能迅速、高效地提高DNA所表达的目的蛋白的性状及表征，是基因工程研究工作中一种非常有用的手段，也是研究蛋白质结构和功能之间复杂关系的有力工具。

发明内容：

[0005] 本发明提供的技术方案之一，是一种香树脂醇合酶突变体，所述的香树脂醇合酶突变体，是在SEQ ID NO.1所示的野生型香树脂醇合酶基础上，发生如下突变中的至少一种获得的：

[0006] (1)将SEQ ID NO.1所示氨基酸序列第323位的亮氨酸替换为丙氨酸；或

[0007] (2)将SEQ ID NO.1所示氨基酸序列第328位的亮氨酸替换为丙氨酸；或

[0008] (3)将SEQ ID NO.1所示氨基酸序列第331位的苯丙氨酸替换为丙氨酸；或

[0009] (4)将SEQ ID NO.1所示氨基酸序列第341位的半胱氨酸替换为丙氨酸。

[0010] 进一步地，将氨基酸序列如SEQ ID NO.1所示的香树脂醇合酶的第323位亮氨酸替换为丙氨酸时，突变体的氨基酸序列如SEQ ID NO.2所示。

[0011] 进一步地，将氨基酸序列如SEQ ID NO.1所示的香树脂醇合酶的第328位亮氨酸替换为丙氨酸时，突变体的氨基酸序列如SEQ ID NO.3所示。

[0012] 进一步地，将氨基酸序列如SEQ ID NO.1所示的香树脂醇合酶的第331位苯丙氨酸替换为丙氨酸时，突变体的氨基酸序列如SEQ ID NO.4所示。

[0013] 进一步地，将氨基酸序列如SEQ ID NO.1所示的香树脂醇合酶的第341位半胱氨酸替换为丙氨酸时，突变体的氨基酸序列如SEQ ID NO.5所示。

[0014] 本发明提供的技术方案之二，是编码上述香树脂醇合酶突变体的基因；

[0015] 进一步地，所述香树脂醇合酶突变体具有SEQ ID NO.7、SEQ ID NO.8、SEQ ID NO.9或SEQ ID NO.10任一所示的编码基因。

[0016] 本发明提供的技术方案之三，是携带上述基因的重组质粒；

[0017] 进一步地，所述重组质粒采用的表达质粒包括但不限于pYLEX1、pUG6等。

[0018] 本发明提供的技术方案之四，是表达上述突变体的重组菌；

[0019] 进一步地，所述重组菌采用的宿主细胞包括但不限于解脂耶氏酵母、酿酒酵母、乳酸克鲁维酵母、大肠杆菌等；

[0020] 更进一步地，所述重组菌采用的宿主细胞为解脂耶氏酵母Po1gΔKU70；

[0021] 优选地，所述重组菌以解脂耶氏酵母Po1gΔKU70为宿主，采用pYLEX1质粒对SEQ ID NO.7-10中的任一基因进行表达。

[0022] 本发明提供的技术方案之五，是上述重组菌在生产香树脂醇中的应用。

[0023] 本发明的有益效果：

[0024] 本发明通过分子对接模拟确定香树脂醇合酶和底物2,3-氧化角鲨烯结合口袋和关键氨基酸残基，并通过定点突变改变蛋白质分子与底物结合位点的氨基酸残基，提高香树脂醇合酶催化效率，进一步提高香树脂醇的产量。同时本发明第一次将CrMAS基因在解脂耶氏酵母中进行异源表达。本发明构建的香树脂醇合酶突变体通过在解脂耶氏酵母中表达，与出发菌株即未突变菌株相比α-香树脂醇和β-香树脂醇的产量均有所提升，其中α-香树脂醇的产量最多提升12.38倍，β-香树脂醇的产量最多提产7.99倍。改造后的基因工程菌株，更适合工业应用，可降低生产成本，提高生产效率。

附图说明：

[0025] 图1为香树脂醇合酶和2,3-氧化角鲨烯结合示意图；

[0026] 图2为香树脂醇合酶和2,3-氧化角鲨烯在site1位点结合示意图；

[0027] 图3为香树脂醇合酶突变质粒核酸凝胶电泳验证图

[0028] M,marker;1～5分别为:pYLCrMAS,pYLC323,pYLC328,pYLC331,pYLC341；

[0029] 图4含有突变前、后香树脂醇合酶的阳性转化子的核酸凝胶电泳验证图

[0030] M,marker;1～5分别为:Po1g KCrMAS,Po1g KC323A,Po1g KC328A,Po1g KC331A,Po1g KC341A；

[0031] 图5为突变后香树脂醇产量变化示意图

[0032] 未突变菌株代表Po1g KCrMAS菌株、323代表Po1g KC323A菌株、328代表Po1g KC328A菌株、331代表Po1g KC331A菌株、341代表Po1g KC341A菌株。

具体实施方式：

[0033] 下面结合实施例对本发明的技术内容做进一步说明。需要说明的是，在不冲突的情况下，本发明中的实施例仅为本发明中的一部分实施例，而不是全部的实施例。基于本发明的实施例，本领域普通技术人员在没有做出创造性劳动前提下所获得的其他实施例，都属于本发明保护范围之内。

[0034] 在本发明中采用如下定义：

[0035] 1.氨基酸和DNA核酸序列的命名法

[0036] 使用氨基酸残基的公认IUPAC命名法，用三字母代码形式。DNA核酸序列采用公认IUPAC命名法。

[0037] 2.香树脂醇合酶突变体的标识

[0038] 采用“原始氨基酸位置替换的氨基酸”来表示CrMAS突变体中突变的氨基酸。如Leu323Ala,表示位置323的氨基酸由野生型的Leu替换成Ala,位置的编号对应于SEQ ID No.1中野生型CrMAS的氨基酸序列编号。

[0039] 在本发明中,CrMAS代表野生型香树脂醇合酶,Leu323Ala、Leu328Ala、Phe331Ala、Cys341Ala分别代表四种突变体,具体信息如下表。

[0040]

香树脂醇合酶	氨基酸突变位点	氨基酸SEQ ID NO.	核苷酸SEQ ID NO.
CrMAS	—	1	6
Leu323Ala	Leu323Ala	2	7
Leu328Ala	Leu328Ala	3	8
Phe331Ala	Phe331Ala	4	9
Cys341Ala	Cys341Ala	5	10

[0041] 以下将结合附图和实施例对本发明作进一步地解释说明。

[0042] 实施例1长春花来源香树脂醇合酶结构模拟和2,3-氧化角鲨烯结合口袋分子模拟

[0043] 以香树脂醇合酶基因(GenBank:AFJ19235)为模板,使用Schrödinger软件Protein Preparation Wizard Panel模块导入CrMAS蛋白三维结构,采用Schrödinger软件Sitemap模块对CrMAS蛋白上的结合口袋进行预测,如图1,从对接得分来看,一共有五处结合良好的位点,其中2,3-氧化角鲨烯与Site 1的结合力最强,细节图如图2,故选择该口袋进行定点突变。

[0044] 实施例2香树脂醇合酶菌株和定点突变菌株的获得

[0045] 1)根据已知的香树脂醇合酶基因经密码子优化后(SEQ ID NO.6),将其导入pYLEX1质粒中,构建获得含有香树脂醇合酶基因的重组质粒pYLEX1-CrMAS。香树脂醇合酶基因通过基因合成获取,重组质粒的构建采用本领域的常用方法即可。

[0046] 2)采用全质粒定点突变的方法获得香树脂醇合酶突变体基因。以pYLEX1-CrMAS质粒为模板,利用Primer Premier 5.0进行引物设计,设计引物序列如下表:

[0047]

Primer		序列(5’-3’)
扩增 Leu323Ala 编码基因	323-F	GCCCTGTGGGACACCCTGAACTACTTCTCTGAGCC
	323-R	GTCCTGGATGAAAGAGTGGGGGTAATACAGGTCGT
扩增 Leu328Ala 编码基因	328-F	GCCAACTACTTCTCTGAGCCCGTGATGCGACGA
	328-R	GGTGTCCCACAGCAGGTCCTGGATGAAAGAG
扩增 Phe331Ala 编码基因	331-F	GCCTCTGAGCCCGTGATGCGACGATGG
	331-R	GTAGTTCAGGGTGTCCCACAGCAGGTCCT
扩增 Cys341Ala 编码基因	341-F	GCCAATAAGATCCGAGAGAAGGCCATGCGAAAGTGC
	241-R	GGGCCATCGTCGCATCACGGGCT

[0048] 3)PCR扩增目的基因:

[0049] 反应体系为:(采用Q5定点突变试剂盒)

[0050]

组分	体积
ddH_2O	8.5μL

pYLEX1-CrMAS	0.5μL
上游引物	0.35μL
下游引物	0.35μL
KOD	0.25μL
dNTP	1.25μL
10×BufferiPCR	1.25μL

[0051] 反应程序为：

[0052]

程序步骤	反应温度	反应时间	

[0053]

Step 1	94℃	2min	
Step 2	98℃	10s	8 个循环
Step 3	68℃	10min	
Step 4	10℃	5min	

[0054] PCR产物加入0.25μL的DpnI消化去除甲基化，然后转化E.coli DH5α菌株，培养12小时候挑取单菌落，过夜培养后提质粒并通过DNA测序验证是否成功将香树脂醇合酶的第323亮氨酸、328亮氨酸、331苯丙氨酸、341位半胱氨酸分别替换为丙氨酸，经PCR和测序验证成功得到突变质粒pYLC323，pYLC328，pYLC331，pYLC341(验证图如图3)。

[0055] 其中，突变质粒pYLC323上含有Leu323Ala突变体编码基因；突变质粒pYLC328上含有Leu328Ala突变体编码基因；突变质粒pYLC331上含有Phe331Ala突变体编码基因；突变质粒pYLC341上含有Cys341Ala突变体编码基因。

[0056] 4)将原始质粒pYLEX1-CrMAS和测序正确的突变质粒pYLC323，pYLC328，pYLC331，pYLC341分别转化Po1gΔKU70菌株感受态细胞，待亮氨酸缺陷板上长出可见菌落后，随机挑取单个菌落，过夜培养后提基因组进行PCR验证。经验证，如图4所示，成功得到Po1gKCrMAS菌株和突变菌株Po1g KC323A，Po1g KC328A，Po1g KC331A，Po1g KC341A。

[0057] 其中，突变菌株Po1g KC323A含有突变质粒pYLC323；突变菌株Po1g KC328A含有突变质粒pYLC328；突变菌株Po1g KC331A突变质粒pYLC331；突变菌株Po1g KC341A含有突变质粒pYLC341。

[0058] 所述pYLEX1质粒购于Yeastern Biotech Co.,Ltd.，所述质粒携带有营养缺陷筛选基因亮氨酸表达盒、标记基因Amp、启动子hp4d以及终止子XPR2 term。

[0059] 所述解脂耶氏酵母Po1gΔKU70是在解脂耶氏酵母Po1g菌株中敲除KU70基因获得的，其构建方法参考下述文献:Genetic engineering of an unconventional yeast for renewable biofuel and biochemical production.Journal of Visualized Experiments,2016,115,e54371。

[0060] 实施例3香树脂醇合酶定点突变菌株对香树脂醇产量的影响

[0061] 1)将实施例2构建的菌株：Po1g KCrMAS菌株和突变菌株Po1g KC323A，Po1g KC328A，Po1g KC331A，Po1g KC341A，分别经两次活化后按照接种量1％接种于YPD培养基中，于30℃，250r/min，摇瓶发酵5天。

[0062] 2)所述基因工程菌的活化步骤为：取斜面菌体一环，接种于含25mL种子培养基中，

30℃,225r/min,振荡培养24h后(完成一次活化),以1%的接种量接种于25mL种子培养基,30℃,225r/min,继续振荡培养16h(完成二次活化)。

[0063] 种子培养基为YPD培养基,具体组成为:蛋白胨20g/L,酵母浸粉10g/L,葡萄糖20g/L,余量为水,pH5.7-5.8,115℃,灭菌20min。

[0064] 3)发酵结束后,取10mL菌液,6000r/min,4℃离心5min,弃废液,通过将发酵菌体加等量石英砂和正己烷涡旋震荡20min以萃取香树脂醇。

[0065] 4)将震荡后的菌体、石英砂和正己烷混合物6000r/min,4℃离心5min,取上层有机相过有机膜,气相色谱-质谱联用测定胞内中的香树脂醇含量。

[0066] 其中,上述气相色谱-质谱联用检测条件为:

[0067] 色谱柱HP-5MS(30m×0.25mm×0.25μm,岛津),载气:高纯氦气,流速为1mL/min,进样口温度280℃,升温程序:100℃,10℃/min升到280℃保持20min,溶剂延迟3min,进样量为1μL。

[0068] 5)经过气相色谱检测,具有不同突变位点的香树脂醇合酶的重组菌催化合成香树脂醇的产量变化如下表及图5:

[0069]

菌株名	α-香树脂醇(mg/L)	β-香树脂醇(mg/L)
Po1g ΔKU70	0	0
Po1g KCrMAS	2.391	1.424
Po1g KC323A	29.602	8.280
Po1g KC328A	10.348	11.379
Po1g KC331A	7.206	6.022
Po1g KC341A	17.375	10.546

[0070] 经测定,突变后的香树脂醇合酶在不同程度上催化合成α-香树脂醇和β-香树脂醇的产量均有提高,说明了突变后酶活和与底物的结合能力有一定程度的提高。其中Po1g KC323A对α-香树脂醇作用最大,提高产量达12.38倍,Po1g KC328A对β-香树脂醇作用最大,提高产量达7.99倍。同时和解脂耶氏酵母出发菌株Po1gΔKU70相比,基因工程菌Po1g KC323A、Po1g KC328A、Po1g KC331A、Po1g KC341A菌株在菌种的其他正常功能上未受明显影响。

[0071] 以上所述实施例仅表达了本发明的几种实施方式,其描述较为具体和详细,但并不能因此而理解为对专利范围的限制。应当指出的是,对于本领域的普通技术人员来说,在不脱离本专利构思的前提下,上述各实施方式还可以做出若干变形、组合和改进,这些都属于本专利的保护范围。因此,本专利的保护范围应以权利要求为准。

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[0456] Gln Asp Leu Leu Trp Asp Thr Leu Asn Tyr Phe Ser Glu Pro Val Met
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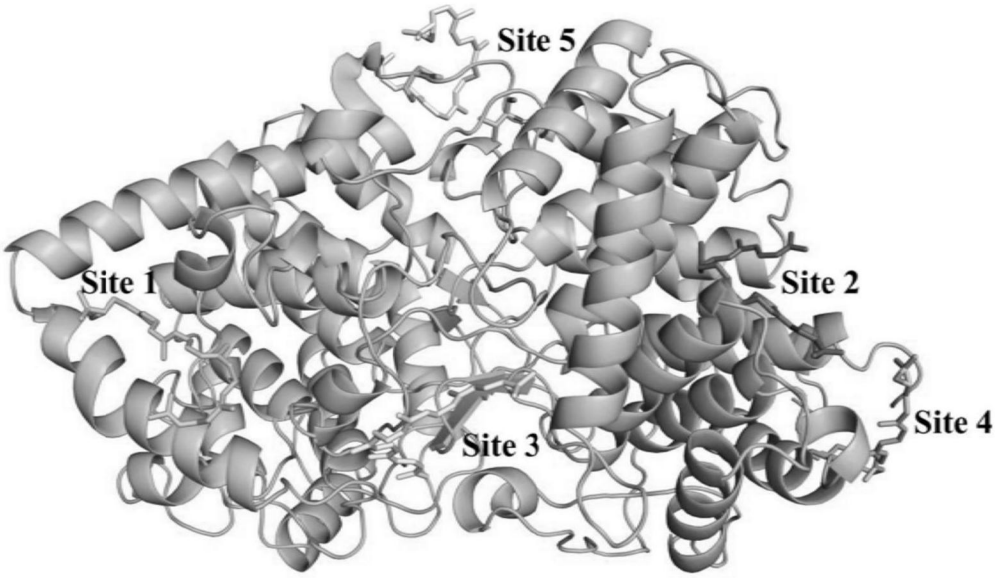
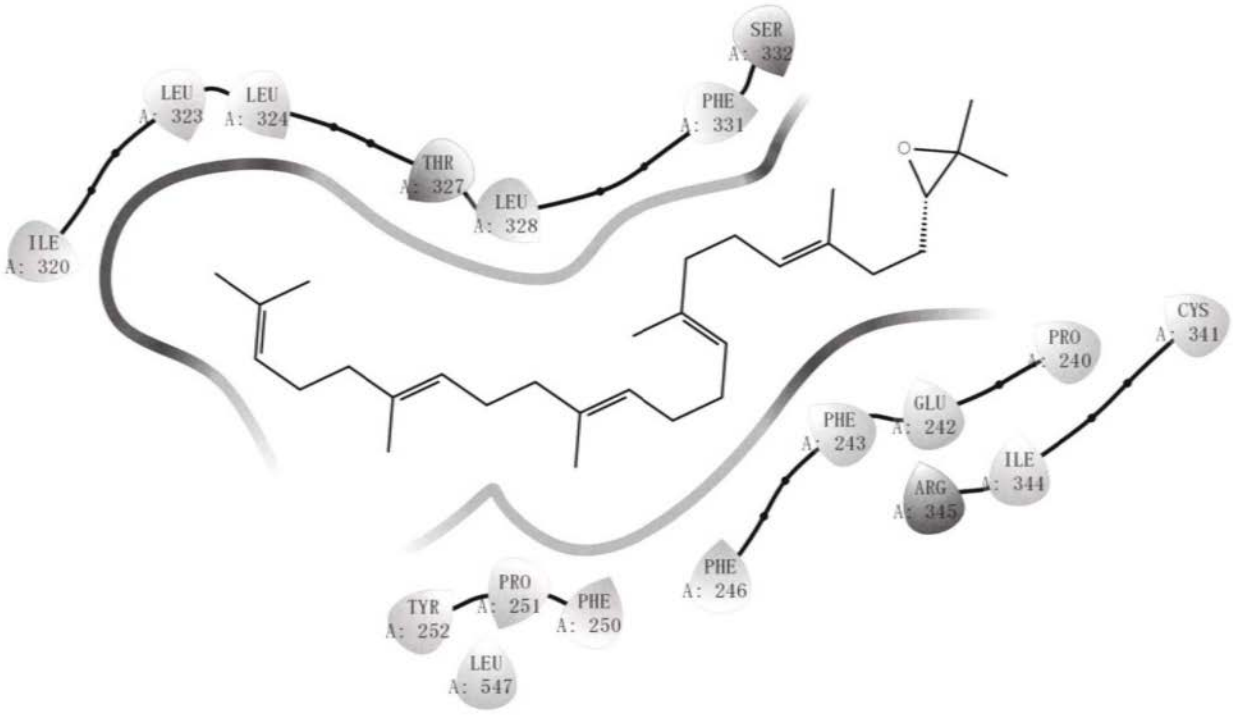

Site 5
Site 1
Site 2
Site 4
Site 3

图1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LEU
A: 323
LEU
A: 324
PHE
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THR
A: 327
LEU
A: 328
ILE
A: 320
CYS
A: 341
PRO
A: 240
GLU
A: 242
PHE
A: 243
ILE
A: 344
ARG
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PHE
A: 246
PRO
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TYR
A: 252
PHE
A: 250
LEU
A: 547

图2

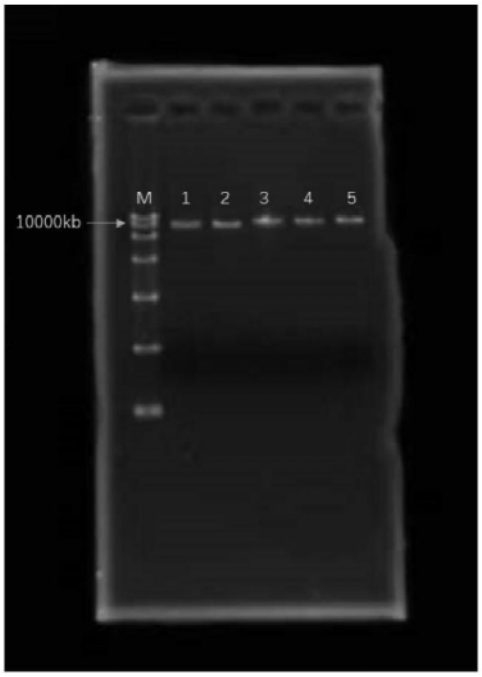

图3

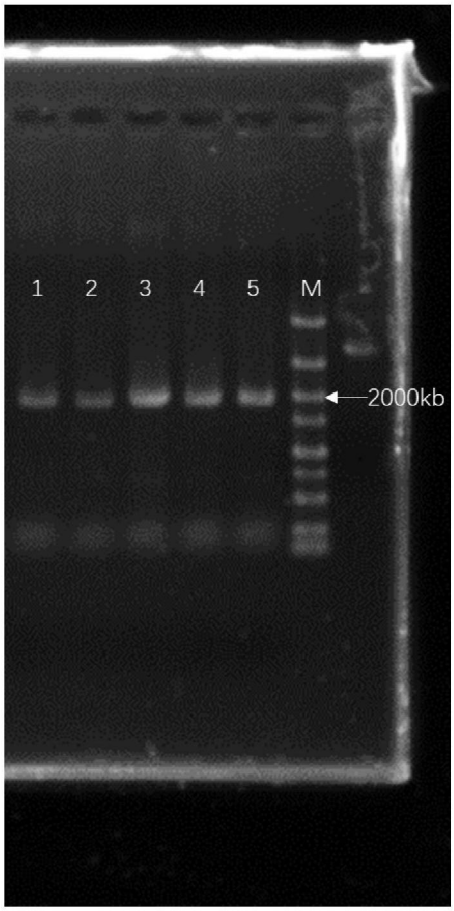

图4

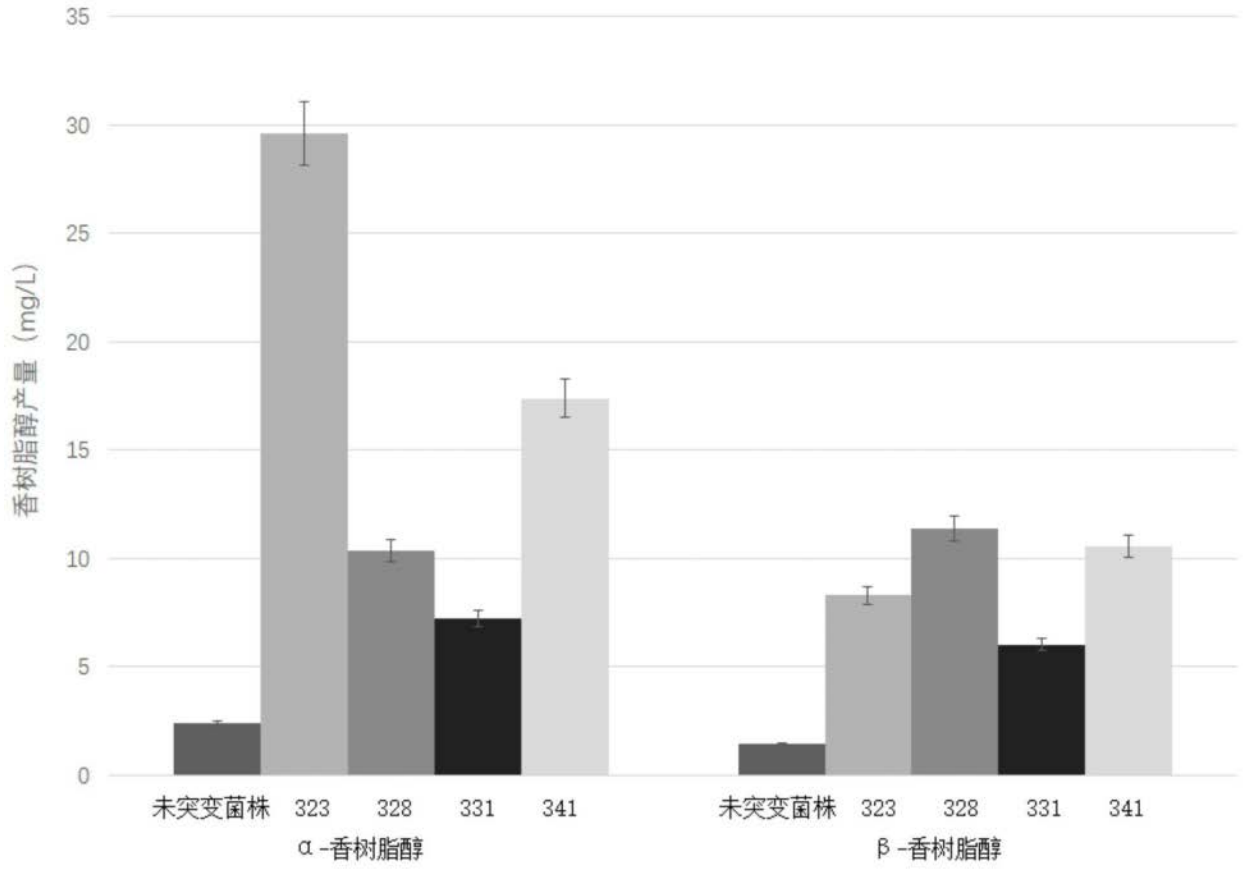
35
30
25
20
15
10
5
0
香树脂醇产量（mg/L）
未突变菌株
323
328
331
341
α-香树脂醇
未突变菌株
323
328
331
341
β-香树脂醇

图5