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Stereoselective synthesis of spiro[5.5]undecane derivatives via biocatalytic [5+1] double Michael additions

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ABSTRACT

A novel enzymatic, promiscuous protocol of D-aminoacylase (DA)-catalyzed [5+1] double Michael addition was developed herein, for the synthesis of (hetero)spiro[5.5]undecane derivatives in moderate yields. It is notable that almost only the *cis* isomers were obtained through this biocatalytic methodology in all the cases according to their ^{1}H and ^{13}C NMR spectra. It is the first report on hydrolase-catalyzed double Michael addition in organic solvent.

1. Introduction

The synthesis of spiro[5.5]undecane and heterospiro[5.5]undecane motifs has engrossed substantial attention from organic chemists for many years, not only because of their unique structural properties [1,2], but also because of their presence in several natural products such as elatol (**I**), isoobtusol (**II**) and (−)-sibirine (**III**) (Fig. 1) [3–8]. Of all the construction methods of the spirocyclics, which can be roughly categorized into alkylation, rearrangement, cycloaddition and cleavage of bridged systems, the alkylation on the quaternary carbon, especially 1,4-addition, is one of the most common methods for the preparation for spiro[5.5]undecane derivatives. However, the conventional methods usually involve bases or Lewis acids as the catalyst under homogeneous conditions, which encountered environmental problems [9–12]. Therefore, the invention and introduction of environmentally compatible catalysts have always showed great importance and attracted enormous attention.

Biocatalysis is a powerful tool for organic synthesis due to its high efficiency, good selectivity and great environmental acceptability [13–16]. The recent progress in catalytic promiscuity of enzymes [17–20] has greatly expanded its application scope. Among them, the Michael addition, widely considered to be one of the most basic and powerful methods for the construction of carbon–carbon and carbon-hetero bonds, has been frequently reported and widely used [18–33]. For instance, our group has demonstrated that D-aminoacylase from *Escherichia coli* (DA) could catalyze the C—C bond formations via Michael additions between α,β-unsaturated carbonyl compounds and activated carbon nucleophiles such as acetylacetone and ethyl acetoacetate [29]. Inspired by this promiscuous behavior, we report a novel discovery that the commercially available DA promotes a cascade [5+1] double Michael addition to form *cis*-spiro[5.5]undecane derivatives in the present work (Scheme 1), yet other types of biocatalyzed double Michael addition has never been reported to the best of our knowledge.

2. Experimental

2.1. Materials

Lipase from *Candida antarctica* (**CALB**) immobilized on acrylic resin (≥10,000 U/g, recombinant, expressed in *Aspergillus oryzae*), Lipase from hog pancreas (**HPL**) (2.4 U/mg, 1 U is the amount of immobilized enzyme which forms 1% octyl laurate from 0.5 mmol lauric acid and 1.0 mmol 1-octanol in 10 ml water-saturated isooctane in 1 h at 20 °C) was purchased from Fluka (Switzerland). D-Aminoacylase from *E. coli* (**DA**) (Not less than 5 MU/g, 1 U is defined as enzyme quantity which produces 1 μmol of D-amino acid per 30 min under the condition as below: 0.1 M *N*-acetyl-D-methionine, pH8.0, 37 °C) was purchased from Amano Enzyme Inc

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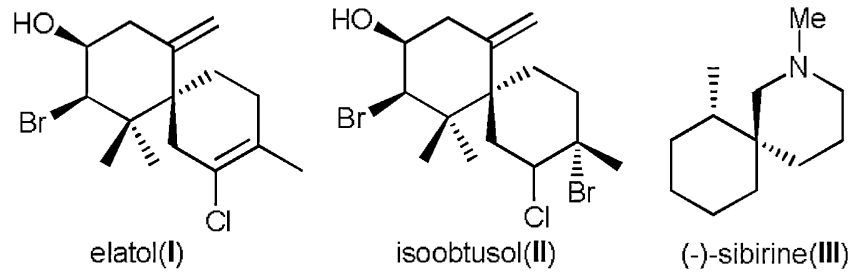
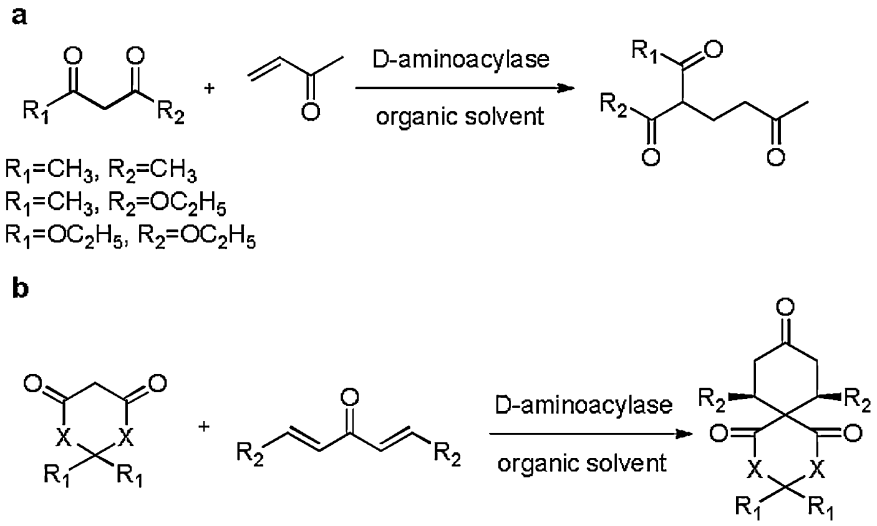


Fig. 1. Some natural products with (hetero)spiro[5.5]undecane.



Scheme 1. (a) DA-catalyzed mono-Michael additions (previous work). (b) DA-catalyzed double Michael additions (this work).

(Japan). All reagents used in the experiments were obtained from commercial sources and used without further purification.

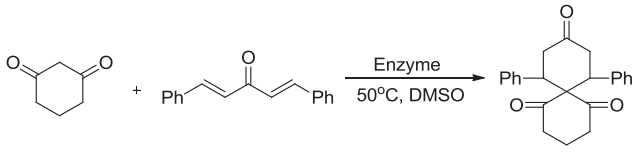
2.2. Analytical methods

The process of reactions was monitored by TLC on silica with Petroleum ether/EtOAc (6/1, v/v) as solvent. The ^{1}H spectra were recorded with TMS as internal standard using a Bruker AMX-400 MHz spectrometer. Chemical shifts were expressed in ppm and coupling constants (*J*) in Hz. Analytical HPLC was performed using a Agilent 1100 series with a reversed-phase Shim-Pack VP-ODS column (150 mm × 4.6 mm) and a UV detector (210 nm). All the known products were characterized by comparing the ^{1}H NMR with those reported in the literature. IR spectra were measured with a Nicolet Nexus FTIR 670 spectrophotometer.

2.3. General procedure for the double Michael additions

1,3-Dione (0.25 mmol), (1E,4E)-1,5-diarylpenta-1,4-dien-3-one (1 mmol), DA (20 mg), DMSO (0.9 ml) and water (0.1 ml) were taken in a flask and the reaction mixture was incubated at 50 °C for 48 or 72 h. Enzyme was filtered off to stop the reaction. CH_2Cl_2 was used to wash the filter paper to assure that products obtained were all dissolved in the filtrate. Then 10 ml of water was added to the filtrate, and the filtrate was extracted with CH_2Cl_2. The organic

Table 1
Double Michael additions catalyzed by various enzymes.[a]



1a 2a 3a .

Entry	Catalyst	Yield (%)
1	Blank	N.R.
2	DA	25 (48[b])
3	Inhibited DA[c]	5
4	BSA	9
5	HPL	8
6	CALB	2

[a] Experimental conditions: 0.25 mmol cyclohexane-1,3-dione (**1a**), 0.25 mmol (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one (**2a**), 20 mg Enzyme, 1 ml DMSO, 50 °C, 48 h. All yields were determined by HPLC. N.R. means no reaction.
[b] 1 mmol (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one (**2a**) was used.
[c] 50 mM $ZnCl_2$ was added to inhibit DA.

Table 2
Screen of reaction conditions of DA-catalyzed double Michael addition of **1a** and **2a**.[a]

Entry	Solvent	Temp. (°C)	Yield (%)
1	DMSO	50	48
2	DMSO (5% water)	50	57
3	DMSO (10% water)	50	61
4	DMSO (15% water)	50	57
5	DMSO (20% water)	50	56
6	DMSO (30% water)	50	19
7	DMSO (10% water)	40	42
8	DMSO (10% water)	60	57
9	DMSO (10% water)	70	54

[a] Experimental conditions: 0.25 mmol cyclohexane-1,3-dione (**1a**), 1 mmol (1E,4E)-1,5-diphenylpenta-1,4-dien-3-one (**2a**), 20 mg DA, 1 ml solvent, 48 h. All yields were determined by HPLC.