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# Enzyme-Catalyzed Cascade Michael/Cyclization Reaction for the Synthesis of 3,4-Dihydropyran Derivatives by Using a Protease

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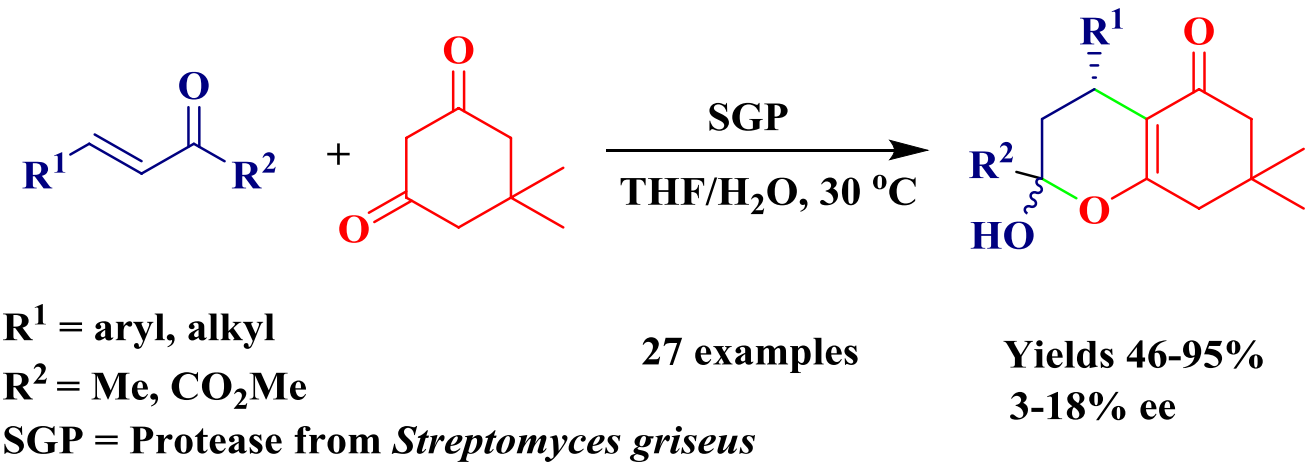
**Abstract**
Protease from *Streptomyces griseus* (SGP) as a sustainable biocatalyst was successfully applied in the Michael/cyclization reaction between dimedone and aryl or alkyl substituted α,β-unsaturated ketones or ester for the synthesis of 3,4-dihydropyran derivatives. The products were obtained in moderate to excellent yields (46–95%) with certain enantioselectivities (up to 18% ee) for 27 examples. This process afforded a potential biocatalytic approach as alternative to chemical synthesis for 3,4-dihydropyran derivatives.

**Graphical Abstract**
Protease from *Streptomyces griseus* (SGP) was used as a catalyst in the Michael addition/cyclization reaction for the synthesis of 3,4-dihydropyran derivatives




**Keywords** Enzyme catalysis · Protease · Enzymatic promiscuity · Michael/cyclization reaction · 3,4-Dihydropyran derivatives

## 1 Introduction

Enzymatic methods constitute a potential complement to the chemical tools in the development of new methodologies in organic synthesis. Enzymes as natural catalysts are safe, non-toxic, renewable and degradable [1]. These advantages make them superior to other chemical reagents in organic synthesis [2]. It is believed that enzymes were generally versatile in ancient times, and they have become more and

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more specific and selective in catalysis through long-time divergence and evolution [3]. However, some promiscuous activities still remain which are often hidden behind a native activity [4–6]. In the recent decades, a good deal of enzymatic promiscuities have been revealed [7–14], and this special aspect of enzymes has attracted growing attention.

Dihydropyran derivatives are widely used in the pharmaceutical and medical fields. Particularly, those with substituents are intriguing building blocks for construction of new biologically active compounds [15, 16]. Thus, some efforts have been devoted toward the development of effective methods for the construction of dihydropyran compounds. In 2003, Jørgensen and co-workers developed the first organocatalytic asymmetric Michael addition of cyclic 1,3-dicarbonyl compounds with α,β-unsaturated enones for the synthesis of dihydropyran derivatives in the presence of an imidazolidine catalyst [17]. After that, chiral bisoxazoline–copper(II) complexes [18], vicinal diamine [19], primary amine derived from quinine [20], cinchona alkaloid-derived pyrimidines [21], chiral diamine catalyst [22], chiral metal–organic framework (MOF) [23], and L-diphenylprolinol trimethylsilyl ether [24] were reported as catalysts for the synthesis of dihydropyran derivatives from similar substrates. Moreover, some other Michael reactions were expanded by many research groups [25, 26]. In 2008, Ma et al. reported diarylprolinol ether/HOAc-catalyzed cascade Michael addition and cyclization of aldehydes and α-keto-α,β-unsaturated esters in water to afford functionalized dihydropyrones [27]. In 2010, Trofimov group successfully applied an acid-catalyzed rearrangement between ketones and acetylene for the synthesis of functionalized 3,4-dihydropyrans [28]. Other Michael/cyclization [29–31], Friedel–Crafts alkylation/cyclization [32], and radical cyclization [33] reactions were also reported.

Recently, several cascade reactions involving Michael/cyclization reaction by enzymatic promiscuity have been reported. In 2011, Lin group reported that acylase from *Aspergillus oryzae* can catalyze the cascade Knoevenagel/Michael/cyclization reaction for the synthesis of 3,4-dihydropyridin-2-ones by condensation of aldehyde with 1,3-dicarbonyl compounds and cyanoacetamide [34]. In 2013, Yu group repored catalytic promiscuity of α-amylase from *Bacillus subtilis* for the asymmetric catalysis of the domino Michael/aldol condensation of salicylaldehyde and α,β-unsaturated ketones [35]. In 2015, our group applied a cascade Michael/cyclization reaction of 2-hydroxychalcones with malononitrile to the synthesis of 2-amino-4*H*-chromene derivatives by using bovine serum albumin as a catalyst [36]. However, biocatalytic synthesis of dihydropyran compounds is rarely reported. In 2014, Ye group reported that the *Escherichia coli* BioH esterase can catalyze the Micheal addition/cyclization cascade reaction of substituted benzalacetones and 1,3-cyclic diketones to prepare dihydropyran compounds with moderate yields (14–76%) without enantioselectivity [37]. In 2015, Yu group found that lipase from *Pseudomonas fluorescens* can catalyze the Micheal addition/cyclization cascade reaction of 1,3-dicarbonyls and α,β-unsaturated aldehydes for the synthesis of 2-hydroxyl-dihydropyran derivatives with moderate yields of 31–75% without enantioselectivity [38].

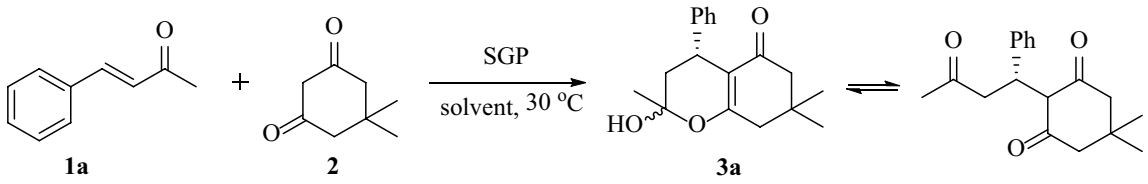
Herein, we report a cascade Michael/cyclization reaction of dimedone to aryl or alkyl substituted α,β-unsaturated ketones or esters catalyzed by protease from *Streptomyces griseus* (SGP) for the synthesis of 3,4-dihydropyran derivatives. The products were obtained in moderate to excellent yields (46–95%) with certain enantioselectivities (up to 18% ee) for 27 examples.

## 2 Results and Discussion

In our initial study, benzalacetone **1a** and dimedone **2** were selected as the model substrates. The SGP-catalyzed model Michael/cyclization reaction was investigated. Because of the diversity of enzyme composition and conformation, enzymes display different catalytic activities in organic solvents [39]. Thus, various solvents were screened (Table 1, entries 1–13). It is worth mentioning that among the tested solvents ether solvents promoted the selectivity of the reaction (Table 1, entries 1–6), and alcohol solvents promoted the reaction yield (Table 1, entries 9 and 10). Weighing the two aspects of yield and selectivity, THF was selected as an optimal solvent.

Then, with the purpose of verifying that the reaction was catalyzed by SGP, some control experiments were performed (Table 1, entries 14–22). In the absence of enzyme, no product was observed for the blank reaction (Table 1, entry 14). Since heavy metal ions usually disturb the three-dimensional structure of enzymes [40], $Cu^{2+}$ was used to pretreat the SGP. It can be seen that $Cu^{2+}$ dramatically decreased the enzyme activity towards the model reaction (yield decreased from 67 to 11%) (Table 1, entry 15). Phenylmethylsulfonyl fluoride (PMSF) is commonly used as a serine protease inhibitor, which binds specifically to the active site serine residue in a serine protease [41], and does not bind to any other serine residue in the protein [42]. Therefore, PMSF as an irreversible inhibitor was used to pretreat the SGP, and the model reaction catalyzed by the PMSF-pretreated SGP only gave the product in a low yield of 9% (Table 1, entry 17). It indicated that PMSF strongly inhibited the activity of SGP in the model reaction, and thus it can be speculated that the natural active center of SGP may be responsible for its activity in the model reaction. Carbonyl diimidazole (CDI) is capable of irreversibly affecting the carboxyl of carboxylic amino acid residues, and it usually used as an inhibitor of enzyme. After pretreated by CDI, the SGP completely

**Table 1** Solvent screening and control experiments




**1a** **2** **3a**

| Entry | Solvent | Yield (%)[a] | ee (%) (R for **3a**)[b] |
|---|---|---|---|
| 1 | THF | 67 | 13 |
| 2 | Diethyl ether | 60 | 13 |
| 3 | Isopropyl ether | 38 | 13 |
| 4 | Anisole | 4 | 12 |
| 5 | 1,4-Dioxane | 31 | 10 |
| 6 | MTBE | 54 | 8 |
| 7 | DMF | 62 | 4 |
| 8 | Ethyl acetate | 45 | 2 |
| 9 | Isopropanol | 77 | 0 |
| 10 | Ethanol | 72 | 0 |
| 11 | MeCN | 57 | 0 |
| 12 | Toluene | 28 | 0 |
| 13 | Water | Trace | – |
| 14 | THF (no enzyme) | 0 | – |
| 15 | THF (SGP pretreated with 0.25 M $Cu^{2+}$)[c] | 11 | 0 |
| 16 | THF [$CuSO_4$ (39.9 mg)] | Trace | – |
| 17 | THF (SGP pretreated with 1.0 M PMSF)[d] | 9 | 2 |
| 18 | THF [PMSF (174 mg)] | Trace | – |
| 19 | THF (SGP pretreated with 1.85 M CDI)[e] | Trace | – |
| 20 | THF [CDI (300 mg)] | Trace | – |
| 21 | THF (SGP pretreated with 0.3 M DEPC)[f] | 18 | 2 |
| 22 | THF [DEPC (43.3 μL)] | Trace | – |

Reaction conditions unless noted otherwise: benzalacetone (0.45 mmol), dimedone (0.30 mmol), and SGP (174 U) in organic solvent (0.9 mL) and deionized water (0.1 mL) at 30 °C for 96 h

[a]Isolated yield

[b]Enantiomeric excess (ee) was determined by HPLC with Chiralpak IA column; absolute configuration of the products were determined by comparison with the known chiral HPLC analysis results [22] (for details, please see the Supporting Information)

[c]SGP (174 U) in $Cu^{2+}$ solution (0.25 M) [$CuSO_4$ (39.9 mg) in deionized water (1 mL)] was stirred at 30 °C for 6 h, and then the water was removed by lyophilization

[d]SGP (174 U) in 1.0 M PMSF solution [PMSF (174 mg) in THF (1 mL)] was stirred at 30 °C for 6 h, and then THF was removed under reduced pressure

[e]SGP (174 U) in 1.85 M CDI solution [CDI (300 mg) in THF (1 mL)] was stirred at 30 °C for 6 h, and then THF was removed under reduced pressure

[f]SGP (174 U) in 0.3 mM DEPC solution [DEPC (43.3 μL) in deionized water (1 mL)] was stirred at 30 °C for 6 h, and then the water was removed by lyophilization

lost its catalytic activity toward the model reaction (Table 1, entry 19). Diethy pyrocarbonate (DEPC) is capable of binding with the imidazole ring of histidine as well as –NH, –SH, or –OH group of protein to inhibit the activity of enzyme. The model reaction catalyzed by DEPC-pretreated SGP only gave the product in a low yield of 18% (Table 1, entry 21). The above control experiments showed that the model reaction was catalyzed by the enzyme, and the active site of SGP may play a key role.

Water can affect the conformation of proteins as well as polarity and stability of the active site of enzyme. Usually enzymes require a certain amount of water to maintain

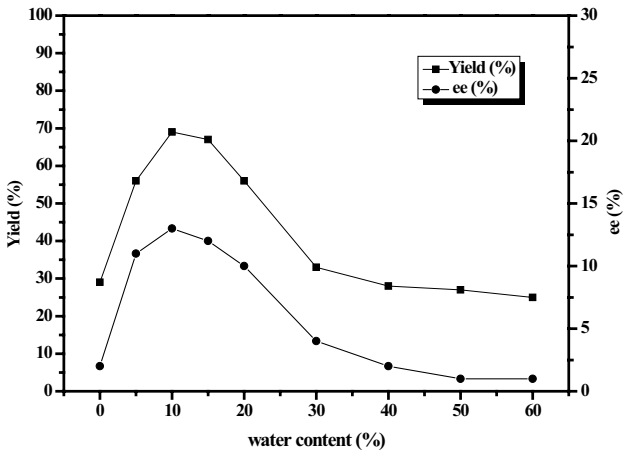



**Fig. 1** Influence of water content on the model reaction. Reaction conditions: benzalacetone (0.45 mmol), dimedone (0.30 mmol), and SGP (174 U) in THF (1.0–0.4 mL) and deionized water (0–0.6 mL) at 30 °C for 96 h. Isolated yield. Enantiomeric excess (ee) (R for **3a**) was determined by HPLC with Chiralpak IA column

their three-dimensional conformation in an organic solvent. Hence, effect of water contents on the model reaction was investigated (Fig. 1). A rapid rise in the yield from 29 to 69% was observed as the water content increased from 0 to 10% [water/(water + THF), v/v]. Higher water content led to a decrease in the yield. The same change trend was found for the enantioselectivity as the water content was increasing. Therefore, 10% of water content was selected as an optimum condition for the reaction.

Next, the volume of reaction medium, the loading of SGP and the molar ratio of substrates were screened to further

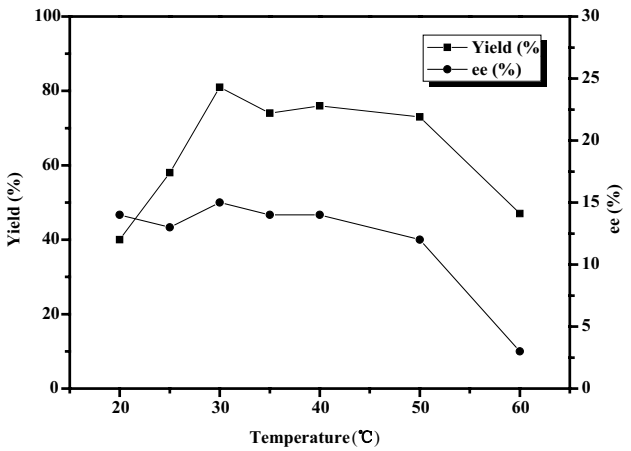


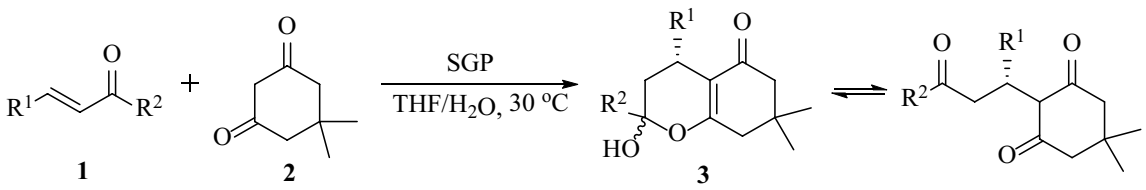

**Fig. 2** Influence of temperature on the model reaction. Reaction conditions: benzalacetone (0.54 mmol), dimedone (0.30 mmol), and SGP (203 U) in THF (0.675 mL) and deionized water (0.075 mL) for 96 h. Isolated yield. Enantiomeric excess (ee) (R for **3a**) was determined by HPLC with Chiralpak IA column

optimize the reaction conditions. The optimal parameters regarding to these aspects were found as the following: 0.75 mL of reaction medium (THF/$H_2O$), 203 U of SGP and 1.8:1 of molar ratio (**1a:2**) were selected for the model reaction on the scale of 0.30 mmol. (For details, please see the Supporting Information)

Temperature is a crucial factor affecting the stability of enzymes. Rising temperature can accelerate the chemical reaction rate, but the high temperature can also inactivate the enzyme through protein denaturation [43]. To obtain the optimum temperature, the effect of temperature on the model reaction in 0.75 mL of THF/$H_2O$ for 96 h was implemented (Fig. 2). Rising temperature from 20 to 30 °C led to a remarkable increase in the yield from 40 to 84%. Higher temperature caused a decrease in the yield, and a rapid drop in the yield was observed when the temperature was above 50 °C. The temperature also showed obvious influence on the enantioselectivity. A significant decrease of ee was observed once the temperature surpassed 50 °C, and a better ee was obtained at 30 °C than other temperatures. Thus, 30 °C was chosen as the optimum temperature for the reaction.

Finally, with the optimal reaction conditions in hand, the generality of the SGP-catalyzed cascade Michael/cyclization reaction for the synthesis of 3,4-dihydropyran derivatives was evaluated using a variety of α,β-unsaturated enones **1** to react with dimedone **2**. Both aryl and alkyl-substituted α,β-unsaturated enones can participate in the reaction well (Table 2, entries 1–27). For aromatic α,β-unsaturated ketones, those with an electron-withdrawing substituent at the para position of benzene ring exhibited higher reactivity than those with an electron-donating substituent at the same position (Table 2, entries 2–9). Among them, 4-benzyloxy and 4-biphenyl substituted aromatic α,β-unsaturated ketones showed much lower reaction efficiency probably due to the dual influences of electron-donating and steric hindrance (Table 2, entries 8 and 9). The electron-withdrawing or electron-donating substituent at the meta position of benzene ring had no apparent effect on the yield (Table 2, entries 10–17). Aromatic α,β-unsaturated ketones with a substituent at the ortho position or with two substituents at ortho and meta positions of benzene ring also can react smoothly with dimedone **2** (Table 2, entries 18–22). Naphthyl or furyl substituted α,β-unsaturated enones performed well in the reaction (Table 2, entries 23 and 24). Furthermore, alkyl-substituted α,β-unsaturated enones were also applicable to the reaction (Table 2, entries 25 and 26). Finally, the α,β-unsaturated ketones which bears a substituent of ester moiety could react with dimedone very well giving the corresponding product in a good yield (Table 2, entry 27). In general, this SGP-catalyzed cascade Michael/cyclization reaction displayed good tolerance to structural and electronic variation of the α,β-unsaturated enones **1** to access a variety of

**Table 2** Substrate scope for the SGP-catalyzed synthesis of 3,4-dihydropyran derivatives




| Entry | $R^1$ | $R^2$ | Product | Time (h) | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | Ph | Me | **3a** | 96 | 88 | 15 |
| 2 | 4-F–$C_6H_4$ | Me | **3b** | 96 | 91 | 16 |
| 3 | 4-Cl–$C_6H_4$ | Me | **3c** | 96 | 66 | 8 |
| 4 | 4-Br–$C_6H_4$ | Me | **3d** | 96 | 85 | 16 |
| 5 | 4-CN–$C_6H_4$ | Me | **3e** | 96 | 81 | 13 |
| 6 | 4-$NO_2$–$C_6H_4$ | Me | **3f** | 96 | 91 | 15 |
| 7 | 4-OMe–$C_6H_4$ | Me | **3g** | 96 | 60 | 7 |
| 8 | 4-BnO–$C_6H_4$ | Me | **3h** | 108 | 49 | 8 |
| 9 | 4-Ph–$C_6H_4$ | Me | **3i** | 144 | 46 | 15 |
| 10 | 3-F–$C_6H_4$ | Me | **3j** | 96 | 66 | 12 |
| 11 | 3-Cl–$C_6H_4$ | Me | **3k** | 108 | 75 | 16 |
| 12 | 3-Br–$C_6H_4$ | Me | **3l** | 96 | 77 | 10 |
| 13 | 3-$CF_3$–$C_6H_4$ | Me | **3m** | 108 | 79 | 18 |
| 14 | 3-$NO_2$–$C_6H_4$ | Me | **3n** | 108 | 77 | 3 |
| 15 | 3-MeO–$C_6H_4$ | Me | **3o** | 96 | 82 | 10 |
| 16 | 3-Me–$C_6H_4$ | Me | **3p** | 108 | 62 | 11 |
| 17 | 3-OH–$C_6H_4$ | Me | **3q** | 96 | 70 | 11 |
| 18 | 2-F–$C_6H_4$ | Me | **3r** | 96 | 71 | 10 |
| 19 | 2-Cl–$C_6H_4$ | Me | **3s** | 96 | 69 | 13 |
| 20 | 2-Br–$C_6H_4$ | Me | **3t** | 96 | 68 | 14 |
| 21 | 2-MeO–$C_6H_4$ | Me | **3u** | 108 | 62 | 14 |
| 22 | 2,3-$(MeO)_2$–$C_6H_3$ | Me | **3v** | 108 | 58 | 10 |
| 23 | 2-Np | Me | **3w** | 144 | 53 | 13 |
| 24 | 2-Furyl | Me | **3x** | 96 | 95 | 12 |
| 25 | *n*-Pr | Me | **3y** | 108 | 82 | 15 |
| 26 | *i*-Pr | Me | **3z** | 108 | 53 | 5 |
| 27 | Ph | COOMe | **3aa** | 48 | 94 | 4 |

Reaction conditions: **1** (0.54 mmol), **2** (0.30 mmol), and SGP (203 U) in THF (0.675 mL) and deionized water (0.075 mL) at 30 °C.

[a]Isolated yield

[b]Enantiomeric excess (ee) was determined by chiral HPLC; absolute configuration of the products were determined by comparison with the known chiral HPLC analysis

complex 3,4-dihydropyrans **3a**–**3aa** in moderate to excellent yields of 46–95% (Table 2, entries 1–27). Unfortunately, very low enantioselectivity was obtained for all the tested substrates at the moment. The absolute configurations were determined by comparing the chiral HPLC with literature [22, 38, 44] (for details, please see the Supporting Information).

## 3 Conclusion

In summary, a new and convenient enzymatic transformation for the synthesis of 3,4-dihydropyran derivatives via a successive Michael addition/cyclization reaction in a "one-pot" protocol has been developed. A wide range of aryl or alkyl substituted α,β-unsaturated ketones or ester can react with dimedone to afford corresponding products in

moderate to excellent yields. Easily available SGP was used as an environmentally friendly biocatalyst, and the reaction was performed under mild reaction conditions. While this work provides a useful alternative synthesis of 3,4-dihydropyran derivatives, it extends the application of enzymatic promiscuity.

## 4 Experimental Section

### 4.1 Materials

Protease from *S. griseus* was purchased from Sigma-Aldrich. [P5174, Lot#SLBL3111V, powder, 5.8 U/mg. One unit will hydrolyze casein to produce color equivalent to 1.0 μmole (181 μg) of tyrosine per min at pH 7.5 at 37 °C (color by Folin–Ciocalteu reagent)]. α,β-Unsaturated enones and ester were prepared according the literatures [45, 46]. Other chemical reagents and solvents were purchased from commercial vendors, and used without any further purification.

### 4.2 General Procedure for the SGP-Catalyzed Synthesis of 3,4-Dihydropyran Derivatives

A mixture of α,β-unsaturated ketone or ester **1** (0.54 mmol), dimedone **2** (0.30 mmol), SGP (203 U), THF (0.675 mL) and deionized water (0.075 mL) was stirred for the specified time at 30 °C, and monitored by TLC analysis. After completion, the enzyme was filtered out; ethyl acetate was used to wash the residue on the filter paper. The filtrate was concentrated under vacuum. The residue was purified by flash column chromatography on silica gel using a mixture of petroleum ether and ethyl acetate (petroleum ether/ethyl acetate = 3/1–8/1, v/v) as eluent to give the products.

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