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Total Synthesis of Capsaicin Analogues from Lignin-Derived Compounds by Combined Heterogeneous Metal, Organocatalytic and Enzymatic Cascades in One Pot

Mattias Anderson,[a] Samson Afewerki,[b] Per Berglund,[a,*] and Armando Córdova[b,c,d,*]

[a] KTH Royal Institute of Technology, Division of Industrial Biotechnology, School of Biotechnology, AlbaNova University Center, SE-10691 Stockholm, Sweden
Fax: (+46)-8-5537-8468; phone: (+46)-8-790-7037; e-mail: per.berglund@biotech.kth.se
[b] Department of Natural Sciences, Engineering and Mathematics, Mid Sweden University, SE-85170 Sundsvall, Sweden
Fax: (+46)-60-148-802; phone: (+46)-77-197-5000; e-mail: armando.cordova@miun.se
[c] Department of Organic Chemistry, The Arrhenius Laboratory, Stockholm University, SE-10691 Stockholm, Sweden
[d] Berzelii Center EXSELENT on Porous Materials, The Arrhenius Laboratory, Stockholm University, SE-10691 Stockholm, Sweden

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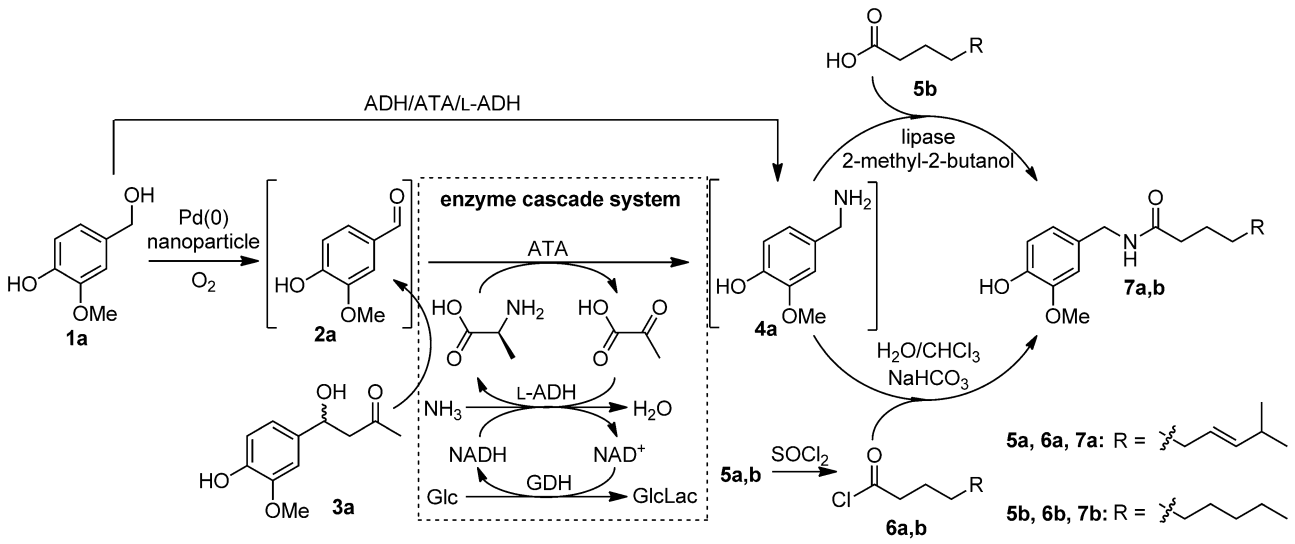
Abstract: The total synthesis of capsaicin analogues was performed in one pot, starting from compounds that can be derived from lignin. Heterogeneous palladium nanoparticles were used to oxidise alcohols to aldehydes, which were further converted to amines by an enzyme cascade system, including an amine transaminase. It was shown that the palladium catalyst and the enzyme cascade system could be successfully combined in the same pot for conversion of alcohols to amines without any purification of intermediates. The intermediate vanillylamine, prepared with the enzyme cascade system, could be further converted to capsaicin analogues without any purification using either fatty acids and a lipase, or Schotten–Baumann conditions, in the same pot. An aldol compound (a simple lignin model) could also be used as starting material for the synthesis of capsaicin analogues. Using L-alanine as organocatalyst, vanillin could be obtained by a retro-aldol reaction. This could be combined with the enzyme cascade system to convert the aldol compound to vanillylamine in a one-step one-pot reaction.

Keywords: aldol reaction; amine transferase; biocatalysis; capsaicin analogues; oxidation; palladium; renewable resources

Capsaicin (**7a**) is a pungent compound found in *Capsicum* spp, and is responsible for the hot and spicy taste of the red pepper fruits of these plants (Scheme 1).[1] Several capsaicin analogues **7** (or capsaicinoids) can also be found in *Capsicum* spp, but capsaicin is one of the most commonly occurring and also the first one to be isolated and have its structure determined.[1–4] Applications of capsaicinoids include spicy foods, self-defense weapons (such as pepper spray) and analgesics such as Zostrix and Axsain. Capsaicinoids have also been shown to have a variety of other physiological effects, for example, activation of both heat loss and heat production,[5] increase of adrenal catecholamine secretion[6,7] and suppression of body fat accumulation.[7,8] Capsaicinoids also show cancer-suppressing properties (see ref.[9] for reviews on the subject).

Capsaicinoids (**7**) can be isolated from natural sources (e.g., *Capsicum* spp pepper fruits), but this gives predominantly capsaicin (**7a**) and dihydrocapsaicin since many of the other capsaicinoids are present only in trace amounts.[3,4] Chemical synthesis is thus useful to obtain the more uncommon capsaicinoids such as nonivamide (**7b**), and for making non-natural capsaicinoids.[10] Capsaicinoids can be prepared from vanillin (**2a**) by first reducing vanillin oxime using a mixture of an excess of metal (Zn) and ammonium formate in methanol under reflux to obtain vanillylamine (**4a**).[11] Vanillylamine can then be further reacted with acyl chlorides (**6**) (Schotten–Baumann) to form the final products (**7**).[10,12,13] Alternatively, the amide bond formation can be accomplished by an enzyme-catalysed transformation between vanillylamine and different fatty acid derivatives.[14]



Scheme 1. Overview of the total synthesis of capsaicinoids (**7a**, **7b**) from compounds **1a**, **2a** and **3a**. In the central enzyme cascade system, an amine transaminase (ATA) is used to convert vanillin (**2a**) to vanillylamine (**4a**) using L-alanine as amine donor. L-Alanine is then regenerated with an L-alanine dehydrogenase (L-ADH). This enzyme is NADH-dependent, and NADH is regenerated with a glucose dehydrogenase (GDH) which converts D-glucose (Glc) into D-glucono-δ-lactone (GlcLac). The amide (**7a**, **7b**) is then formed in the same pot, either by a lipase-catalysed reaction between vanillylamine and a fatty acid (**5b**), or by reacting vanillylamine with acyl chlorides (**6a**, **6b**), resulting in the final product (**7a**, **7b**). The synthesis can also be started from vanillyl alcohol (**1a**) through Pd(0) nanoparticle-catalysed aerobic oxidation to vanillin which is then used directly for the synthesis of capsaicinoids in the same pot. Alternatively, another enzyme cascade system including an alcohol dehydrogenase (ADH), an amine transaminase and an L-alanine dehydrogenase (ADH/ATA/L-ADH system, for details see Scheme 2) can be used to convert vanillyl alcohol to vanillylamine. Another option is to start from an aldol compound **3a** (a simple lignin model), which then undergoes retro-aldol transformation catalysed by alanine followed by transamination using the same alanine as amine donor in a one-step one-pot reaction.

Lignin derived from wood is a natural source for the production of vanillyl alcohol (**1a**) and vanillin (**2a**) (Scheme 1),[15] and it is therefore a possible raw material for the synthesis of capsaicinoids (**7**). Lignin is especially interesting since it is renewable, available in large quantities in Nature and currently only used for a limited number of applications.[15,16]

The objective of this study was to develop a new more sustainable process for the total synthesis of capsaicinoids by using renewable resources and multicatalytic cascade relay[17] sequences. The first goal of the project was to use an enzymatic approach to prepare the intermediate vanillylamine (**4a**), since this would eliminate the need to use a metal[11,12] for the reductive amination step. The second goal was to use various renewable compounds as starting materials for the synthesis. The third and final goal was to perform the synthesis in one pot, eliminating the need for isolation of intermediates and reducing the amount of waste formed in the process. Thus, in order to achieve these goals, a method for combining enzymes with various other catalysts such as metals and organocatalysts in the same pot had to be developed. Such a method would be of more general interest and not only useful for capsaicinoid synthesis.

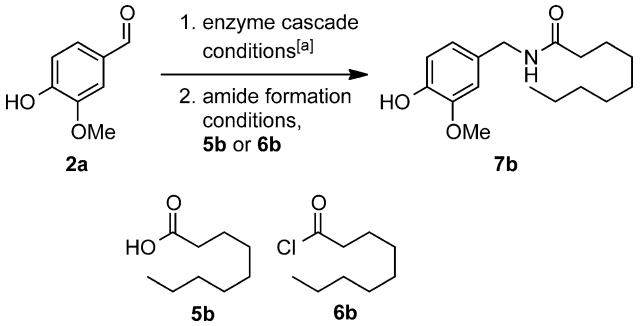
An enzymatic approach using an amine transaminase (ATA, EC 2.6.1.18)[18] was chosen for preparation of vanillylamine (**4a**) from vanillin (**2a**). The ATA-catalysed reaction can then be combined with either acyl chlorides (**6**) under Schotten–Baumann conditions,[13] or an enzymatic approach using a lipase and fatty acids (**5**),[14] to conclude the total synthesis of capsaicinoids in one pot (Scheme 1).

The amine transaminase from *Chromobacterium violaceum*[19] has been reported to accept vanillin (**2a**) as a substrate.[20] Initial experiments showed that vanillin can indeed be converted to vanillylamine (**4a**) by this ATA, but the conversion was only 25% despite a large excess (50 equiv.) of the amine donor L-alanine. In order to increase the conversion without using a large excess of amine donor, an enzyme cascade system previously described by Koszelewski et al.[21] and Truppo et al.[22] was applied (Scheme 1). In the transamination reaction, the amine donor L-alanine is converted to pyruvate. An L-alanine dehydrogenase (L-ADH, EC 1.4.1.1) was added to the reaction system to convert the formed pyruvate back to L-alanine, thus shifting the equilibrium towards product formation by removing the pyruvate co-product and regenerating the amine donor. The nitrogen source used to convert pyruvate to L-alanine is ammonia, which then becomes the overall amine donor for the amine transaminase reaction since the L-alanine is regenerated. L-ADH requires NADH as a cofactor

for this reaction, so therefore another enzyme, glucose dehydrogenase (GDH, EC 1.1.1.47), was added to regenerate NADH. The overall cascade system thus converts one equivalent of vanillin into vanillylamine by consuming one equivalent of ammonia and one equivalent of glucose. This system was successfully applied to prepare vanillylamine from vanillin (50 mM) in a 1 mL scale, with a conversion of 95% after 17 h.

In the next step, methods for formation of the amide bond in the final capsaicinoid product (**7**) were investigated. Initial experiments showed that Schotten–Baumann conditions[13] could convert pure vanillylamine (**4a**) into capsaicin (**7a**) and nonivamide (**7b**) in 91% and 94% isolated yields, respectively (Scheme 1). Acyl chlorides (**6a**, **6b**) were prepared from the acids (**5a**, **5b**) using $SOCl_2$. With this method, the total synthesis of nonivamide from vanillin (**2a**) was performed in one pot. The enzyme cascade system was successfully scaled up to give 100 mg vanillylamine after 19 h ($c > 99\%$). Next, sodium bicarbonate was added to the flask followed by chloroform and the acyl chloride **6b** to give pure nonivamide in an overall yield of 92% from vanillin after silica-gel column chromatography (Table 1). As an alternative to the Schotten–Baumann process, a lipase (EC 3.1.1.3) can be used to catalyse the amide formation.[14] First, the enzyme cascade system converted vanillin to vanillylamine with a conversion of 94% after 22 h. The reaction mixture was lyophilised, followed by addition of the fatty acid **5b** and the lipase in 2-methyl-2-butanol to give nonivamide with an isolated yield of 52% after a 48 h reaction (Table 1).

Table 1. Results for the synthesis of nonivamide (**7b**) from vanillin (**2a**) in a one-pot cascade reaction (see Scheme 1 for details).



Entry	Amide formation conditions	Yield[b]
1	**6b**, $NaHCO_3$, $H_2O/CHCl_3$	92%
2	**5b**, lipase, 2-methyl-2-butanol	52%

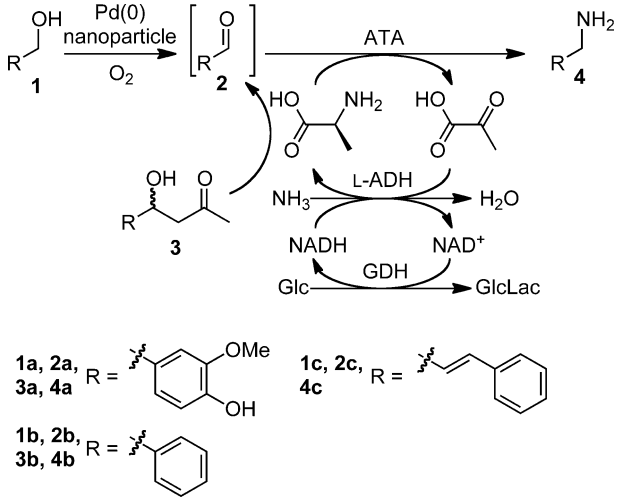
[a] L-Alanine, NH_3, D-glucose, NADH, amine transaminase (ATA), L-alanine dehydrogenase (L-ADH), glucose dehydrogenase (GDH), H_2O, for details see Scheme 1.
[b] Yield after silica gel column chromatography

To further explore the possibility of using renewable raw materials for the synthesis of capsaicinoids (**7**), two compounds that can be derived from lignin (compound **1a** and a simple lignin model **3a**) were investigated as possible starting materials for the total synthesis (Scheme 1). The goal was still to perform the reactions in one pot, and therefore it was necessary to find ways to combine the previously described enzyme cascade system (Scheme 1) with systems for obtaining vanillin (**2a**) from vanillyl alcohol (**1a**) or the aldol compound **3a**.

The first approach was to use Pd(0) nanoparticles[23] for the aerobic oxidation of vanillyl alcohol (**1a**) to vanillin (**2a**). The vanillin can then be further converted to vanillylamine (**4a**) using the enzyme cascade system as described earlier (Scheme 1). The main challenge here was to get the palladium catalyst and the enzyme cascade system to work together under the desired one-pot conditions. The Pd(0) nanoparticles were prepared as described in the Supporting Information or purchased from commercial sources. The synthesised heterogeneous Pd nanoparticles were selected since they exhibit excellent stability and recyclability without leaching in the presence of organocatalysts or a lipase enzyme.[23] The Pd nanoparticle-catalyzed aerobic oxidation was rapid and smooth and full conversion from vanillyl alcohol to vanillin (> 99%) was reached within as little as 2 h and 3 h when Pd on controlled pore glass (CPG) and Pd on mesocellular foam (MCF), respectively, were used as the catalysts. In comparison, commercially available heterogeneous Pd(0)/C did only produce 43% of **2a** from **1a** after 24 h. Next, the enzyme cascade system was added directly to this crude mixture, resulting in a vanillin starting concentration of 1.5 mM after dilution. The reaction was slower compared to when pure vanillin was used but still reached high conversion. After 44 h, vanillylamine was obtained with an overall conversion of 87% from vanillyl alcohol (Table 2). It is noteworthy that the three enzymes (ATA, L-ADH and GDH) could catalyse their cascade reaction in the presence of the heterogeneous transition metal catalyst. To show that this system is not limited to only vanillyl alcohol, the same conditions were used to convert two other primary alcohols, **1b** and **1c**, into the corresponding amines, **4b** and **4c** respectively (Table 2). Compound **4b** was obtained with an overall conversion of 30% from **1b**, while compound **4c** was obtained with an overall conversion of 84% from **1c**.

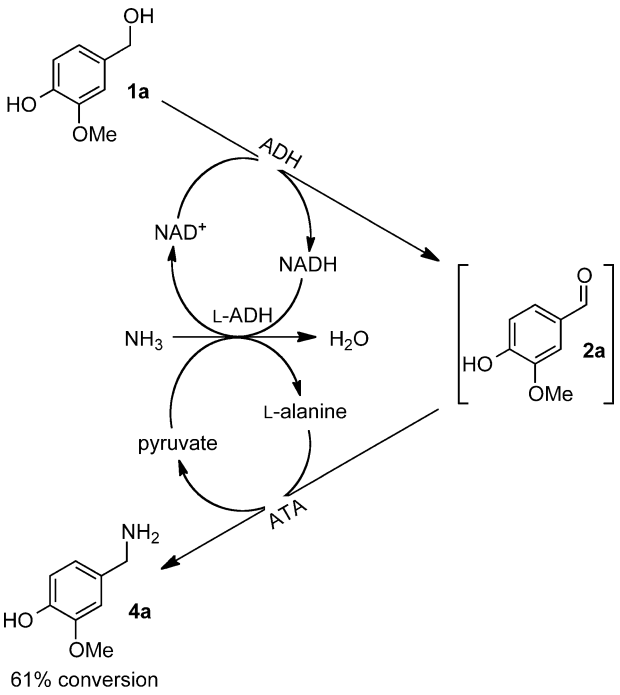
As an alternative to the Pd oxidation process, an alcohol dehydrogenase (ADH, EC 1.1.1.1) can be used together with the ATA to convert vanillyl alcohol (**1a**) to vanillylamine (**4a**). Sattler et al. previously described how these enzymes can be combined with an L-ADH for conversion of primary alcohols to amines.[24] A similar system was applied for the preparation of vanillylamine from vanillyl alcohol

Table 2. Results for the preparation of amines from alcohols or aldol compounds in a one-pot cascade reaction.



Starting material	Main product	Conversion to main product[a]
1a	**4a**	87%
1b	**4b**	30%
1c	**4c**	84%
3a	**4a**	40%
3b	**4b**	52%

[a] Conversion determined by HPLC analysis. See the Supporting Information for experimental details.



Scheme 2. Overview of the ADH/ATA/L-ADH cascade system used to convert vanillyl alcohol (**1a**) to vanillylamine (**4a**). First, vanillyl alcohol is converted to vanillin (**2a**) by an alcohol dehydrogenase (ADH), also converting NAD^+ to NADH. Vanillin is then further converted to vanillylamine by an amine transaminase (ATA), also converting L-alanine to pyruvate. An L-alanine dehydrogenase is used to regenerate both NAD^+ and L-alanine, also shifting the equilibrium towards vanillylamine production by removing the two co-products.

(Scheme 2). Here, vanillyl alcohol is first oxidised to vanillin (**2a**) by the ADH. This process also reduces the cofactor NAD^+ to NADH. Vanillin is then converted to vanillylamine by the ATA, using L-alanine as amine donor. Finally, L-ADH serves to regenerate both the L-alanine and NAD^+, a process which also shifts the equilibrium towards product formation since both the NADH and pyruvate co-products are removed. The reaction reached a conversion of 79% after 22 h, where 61% of the vanillyl alcohol (starting concentration 25 mM) had been converted into vanillylamine, and 18% into vanillin (Scheme 2).

For the aldol compound **3a**, the approach was to convert it to vanillin (**2a**) with a retro-aldol transformation. This kind of reaction could be catalysed by an organocatalyst such as L-alanine.[25] If the enzyme cascade system described earlier (Scheme 1) is used, the same L-alanine could first catalyse the retro-aldol transformation, and then act as amine donor for the transamination step. Thus, L-alanine first catalyses the transformation of compound **3a** to vanillin, which is then further converted to vanillylamine (**4a**) by the enzyme cascade system using the same L-alanine as amine donor. After 90 h, the aldol compound **3a** (2.5 mM) was consumed (>99% conversion) to vanillylamine (**4a**) (40%) and to the dehydration product of **3a** (60%), which was obtained by L-alanine catalysis. Compound **3a** is not a substrate for the ATA, and thus no 1,3-amino alcohol side product was formed. To show that this method is not limited to only compound **3a**, the aldol compound **3b** was converted to benzylamine (**4b**) using the same conditions. After 94 h, all of compound **3b** was consumed and benzylamine was obtained with a conversion of 52% (Table 2).

In conclusion, a new method for the total synthesis of capsaicinoids has been demonstrated. The synthesis was successfully performed in one pot starting from compounds that can be derived from lignin, making the overall process more environmentally friendly. This study also shows how enzyme cascade systems can work together with heterogeneous metal catalysts and organocatalysts in the same pot, a concept which could be useful not only for capsaicinoid synthesis but also for various other processes where several different catalysts are needed.

Experimental Section

Typical Procedure for the Synthesis of Nonivamide (7b) from Vanillyl Alcohol (1a)

Step 1: An oven-dried microwave vial was loaded with vanillyl alcohol (**1a**) (46.3 mg, 0.3 mmol, 1.0 equiv.) and Pd(0) nanocatalyst [Pd(0)-AmP-MCF, 20.1 mg, 0.015 mmol, 8 wt%] or [Pd(0)-AmP-CPG, 500 Å, 90.0 mg, 0.015 mmol, 166 μmol/g] followed by addition of toluene (0.6 mL). Next, the vial was sealed and a balloon filled with O_2 was connected to it and the reaction mixture was stirred at 70 °C. After 3 h [when Pd(0)-AmP-MCF was used] or 2 h [when Pd(0)-CPG, 500 Å was used] the conversion had reached >99% to vanillin (**2a**).

Step 2: Vanillin (**2a**) (99.3 mg, 0.65 mmol, 1.0 equiv.) was dissolved in DMSO (1.31 mL). D-Glucose (352.8 mg, 1.96 mmol, 3.0 equiv.), L-alanine (290.8 mg, 3.26 mmol, 5.0 equiv.) and ammonium chloride (104.8 mg, 1.96 mmol, 3.0 equiv.) were dissolved in 50 mM HEPES buffer (6 mL) in a 50-mL falcon tube, the vanillin solution was added and the pH was adjusted to 8.2 at 37 °C (1 M NaOH). NADH (9.55 mg, 0.013 mmol, 0.02 equiv.), glucose dehydrogenase (GDH) (0.65 mg, 130.6 U) and amine transaminase (ATA) (20.9 mg) were dissolved in 50 mM HEPES buffer (pH 8.2 at 37 °C) and added to the reaction tube, along with L-alanine dehydrogenase (L-ADH) (20 μL, 91.4 U). More HEPES buffer (50 mM, pH 8.2 at 37 °C) was added to give a final volume of 13.06 mL and final concentrations 250 mM L-alanine, 50 mM vanillin, 150 mM ammonium chloride, 150 mM D-glucose, 1 mM NADH and 10% DMSO v/v, together with 1.9 mg/mL ATA, 7 U/mL L-ADH and 10 U/mL GDH. The reaction was performed in 37 °C and darkness with no stirring. After 22 h the conversion to vanillylamine (**4a**) had reached 94% as determined by HPLC analysis. The pH of the solution was adjusted to 12 (1 M NaOH), and the reaction mixture was freeze-dried, in order to remove the water.

Step 3: The dried crude reaction mixture from the previous step (containing vanillylamine 94 mg, 0.62 mmol, 1.00 equiv.) was dissolved in 2-methyl-2-butanol (31 mL, 20 mM). To the reaction was added 4 Å molecular sieves (2 g), compound **5b** (98.7 mg, 0.62 mmol, 1.00 equiv.) and lipase (1.9 g, 20 mg/mL). The reaction was stirred at 45 °C for 48 h. Afterwards the reaction was cooled to room temperature and filtered. The solvent was removed under reduced pressure and the crude material was purified by chromatography to afford nonivamide (**7b**) as a light yellow oil; isolated yield: 52%.

More details and information about other procedures can be found in the Supporting Information.

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