

One-Pot Synthesis of Tricyclic Benzoxazines and Benzoxazepine by Heterogeneous Biochemo Multienzyme Cascade Reaction

Eliana Capecchi,[†] Elisabetta Tomaino,^{*} Bruno M. Bizzarri,[†] and Raffaele Saladino^{*}



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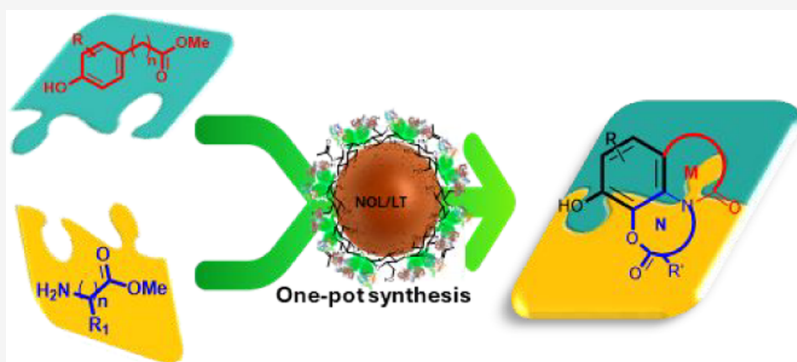
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ABSTRACT: Benzoxazine and benzoxazepine derivatives with tricyclic five-, six-, and seven-membered lactone and lactam rings were synthesized in one-pot conditions by using biochemo multienzyme cascade of lipase M and tyrosinase. The reaction involves tyrosinase-mediated *ortho*-hydroxylation of the phenolic moiety, followed by 1,6-Michael addition and tandem intramolecular ring closure. The method achieves high atom economy, minimizes purification steps, and provides a sustainable alternative to conventional multistep syntheses. Enzymes showed excellent reusability, further enhancing the green approach.

INTRODUCTION

Sustainable synthetic strategies for the synthesis of libraries of privileged heterocycles are paramount in drug design and discovery.¹ We have recently reported a green catalytic procedure for the synthesis of highly functionalized bicyclic 1,4-benzoxazines based on multicomponent biochemo multienzyme cascade reaction.² The cascade was composed of lipase M from *Mucor javanicus* (L) and tyrosinase from *Agaricus bisporus* (T) immobilized on lignin nanoparticles (NOL/LT).^{3–6} The use of NOL in the immobilization of single^{7–11} and multienzymes has been reported,^{3,4} leading to enhanced stability and reactivity.¹² The procedure coupled several synthetic steps,¹³ showing numerous advantages over the alternative step-by-step procedures, as a consequence of the combination of multiple transformations in a unique and sustainable reactive framework. Our interest in the application of biochemo multienzyme cascade to the synthesis of bioactive compounds has given rise to the development of methods for the preparation of flavonoids¹⁴ and Pummerer's ketones.¹⁵ Tricyclic 1,4-benzoxazines are important drugs^{16,17} with several pharmacological effects, including antithrombotic¹⁸ and anticancer (melanoma and leukemia) activities.^{19–21} Benzoxazepines are the structural variant of 1,4-benzoxazine, in which the six-membered lactone ring is replaced by the seven-membered counterpart.²² They are in the top 53 most frequently listed drugs in the FDA Orange Book,²³ representing important

pharmacophores for discovering novel therapeutic candidates.^{24–27} In this context, approved drugs are amoxapine and loxapine,^{28,29} which contain the benzoxazepine core, and levofloxacin and aparenone, characterized by the benzoxazine counterpart.^{30,31} In addition, benzazepinones appear as subunits of shornephine natural products.³² Despite their biological properties, the synthesis of tricyclic 1,4-benzoxazines and 1,5-benzoxazepines still requires harsh and tedious multistep conditions,^{1,19,20} involving laborious purification and isolation procedures (Figure 1, panel A).^{22,30,33–37} Among them, the convergent intermolecular annulation approach is considered the most desirable.³⁸

In order to solve these drawbacks, we describe here the use of biochemo multienzyme cascade NOL/LT for the one-pot synthesis of tricyclic benzoxazine and benzoxazepine under sustainable heterogeneous conditions (Figure 1, panel B).

The retrosynthetic analysis by dissection of desired benzoxazines and benzoxazepines leads to fragments, phenolic

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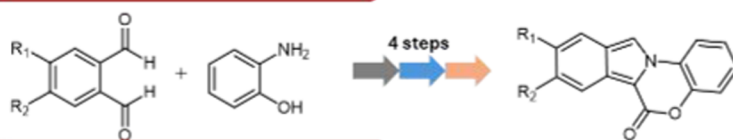
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A. Previous works

(a) Benzoxazine derivatives synthesis ^[34](b) Benzoxazepine derivatives synthesis ^[22]

Limitations:

- Harsh conditions;
- Multi-step reactions;
- Tedious purifications;
- Laborious isolations.

(c) Benzoxazine derivatives synthesis (Levofloxacin) ^[33] PATENTED ^[29]

B. This work:

One-pot synthesis

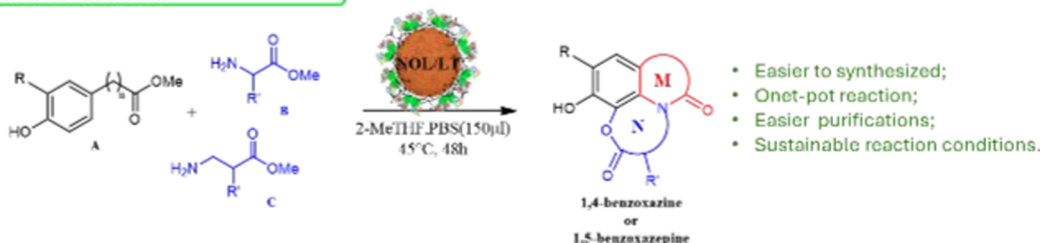
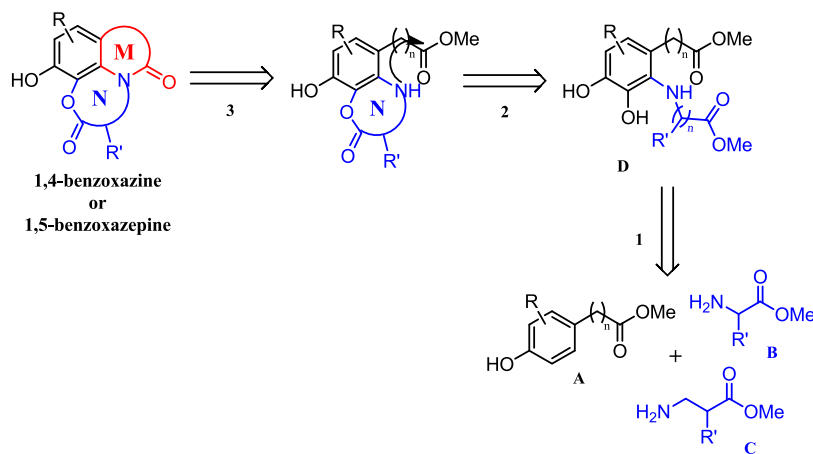


Figure 1. (A) (a) Previous work for the synthesis of tricyclic benzoxazines;³⁴ (b) previous work for the synthesis of tricyclic benzoxazepines;²² (c) previous works for the synthesis of Levofloxacin drug.^{29,33} (B) This work: realization of the proposed transformation.

Scheme 1. Retrosynthetic Analysis for the Synthesis of Tricyclic Benzoxazine and Benzoxazepine Derivatives^a

^aStep 1: oxidative coupling of phenol A with α-amino acid B (pathway for benzoxazine), or β-amino acid C (pathway for benzoxazepines). Steps 2 and 3: Tandem ring closure of the lactone and lactam moieties.

acids A and α-amino acid B (way to benzoxazine), or β-amino acid C (way to benzoxazepine), combined by oxidative 1,6-Michael addition to catechol intermediate D and successive ring closure to lactone N and lactam M (Scheme 1). Among phenolic carboxylic acids, we tested methyl 3-(4-hydroxyphenyl)propanoic acid 1, methyl 2-(4-hydroxyphenyl)acetic acid 2, methyl (Z)-3-(3,4-dihydroxyphenyl)acrylic acid 3, methyl 3-(4-hydroxy-3-methoxyphenyl)propanoic acid 4, methyl 4-(4-hydroxyphenyl)butanoic acid 5, and methyl 2-(3-bromo-4-

hydroxyphenyl)acetate 6. Amino acids were α-amino acid methyl esters 6a–e (glycine 6a, alanine 6b, valine 6c, leucine 6d, and phenylalanine 6e) and β-amino acid methyl esters 6f–g (β-alanine 6f and L-3-aminoisobutyric acid 6g). General remarks are given in SI 1.

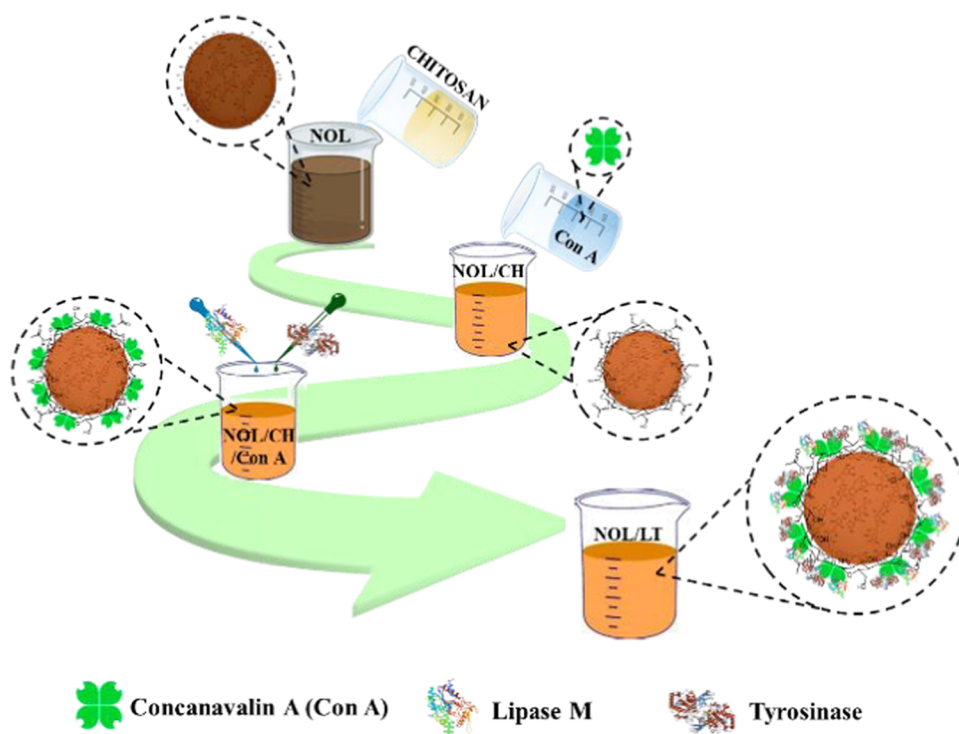
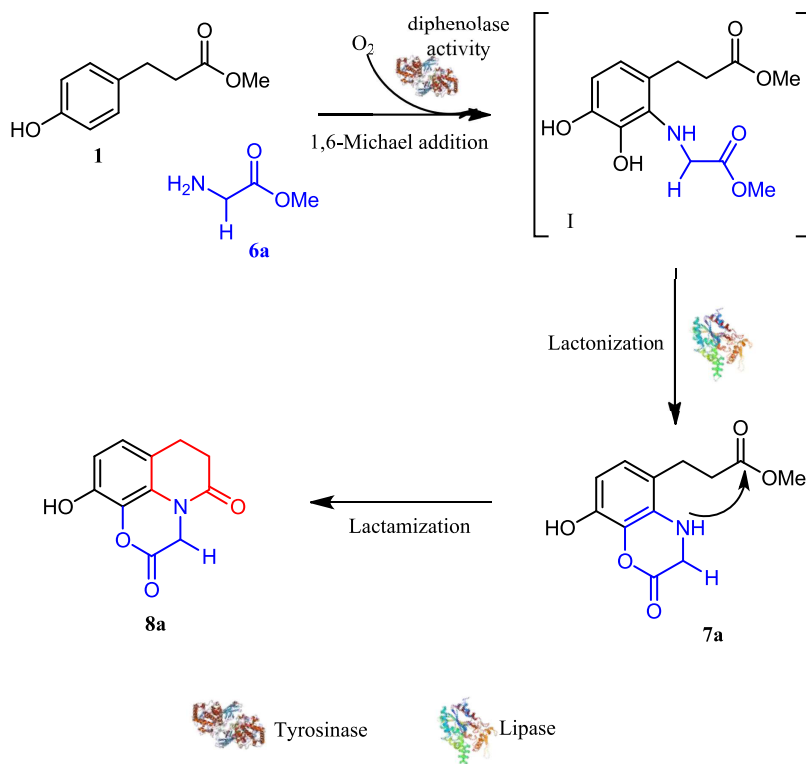


Figure 2. Representation of the NOL/LT preparation.

Scheme 2. Schematic Representation of the Formation of 8a from 1 and 6a

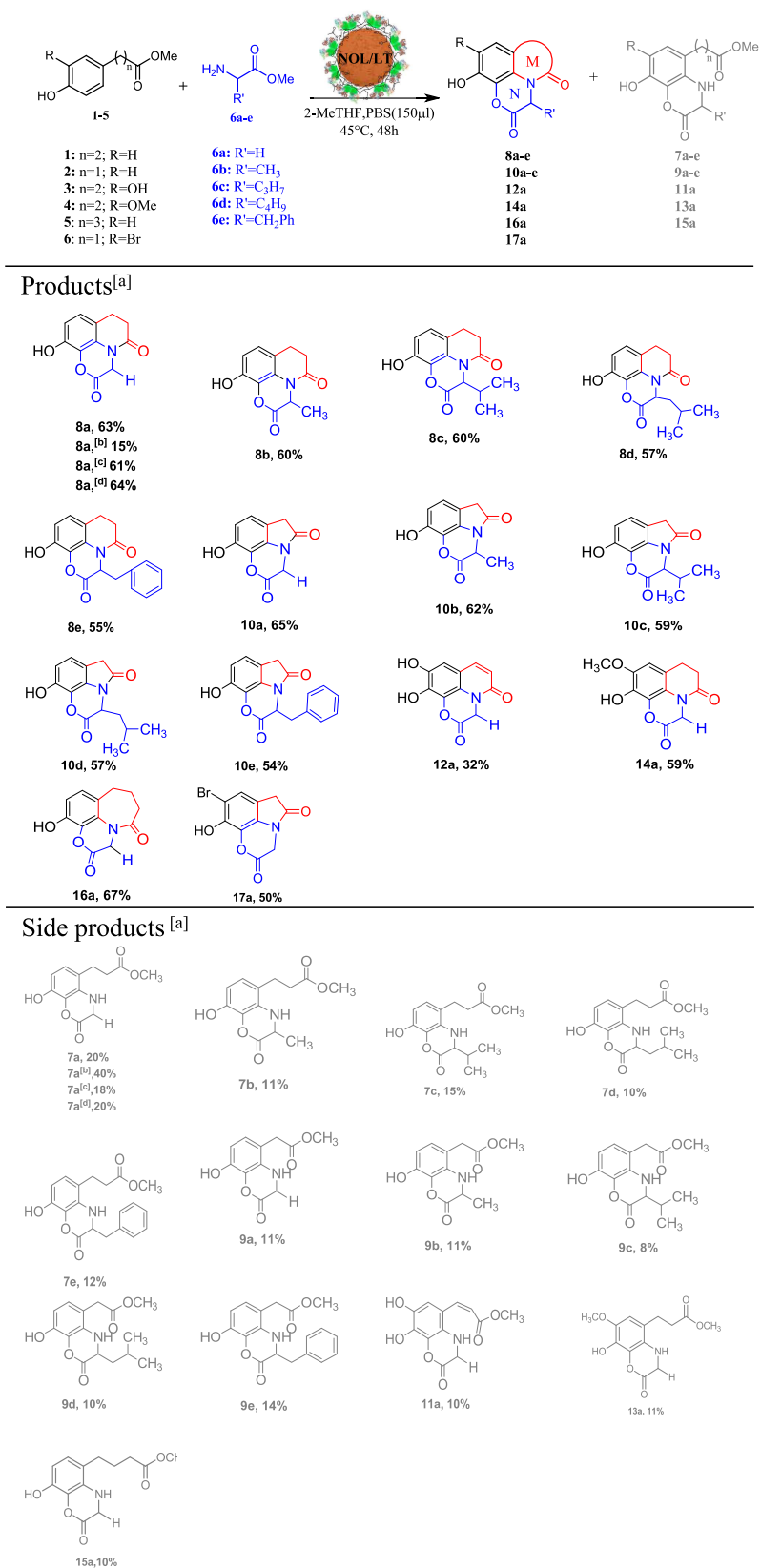


RESULTS AND DISCUSSION

NOL/LT was prepared as reported in ref 2. Briefly, chitosan (CH) was added dropwise to NOL in Milli-Q water under slow magnetic stirring for 2 h at 25 °C to yield the NOL/CH intermediate. Then, NOL/CH were treated with Con A solution (0.5 mL) in PBS (0.1 M, pH 7.0) followed by addition of lipase

M (40 U; 3.0 mg mL⁻¹) and tyrosinase (40 U; 1.0 mg mL⁻¹) to yield NOL/LT (Figure 2). FE-SEM, FT-IR analysis, and kinetic parameters of NOL/LT are reported in SI2.² Con A was applied as an orienting agent for the immobilization of the two enzymes.^{5,6}

Table 1. Synthesis of Tricyclic 1,4-Benzoxazines and Related Side-Products



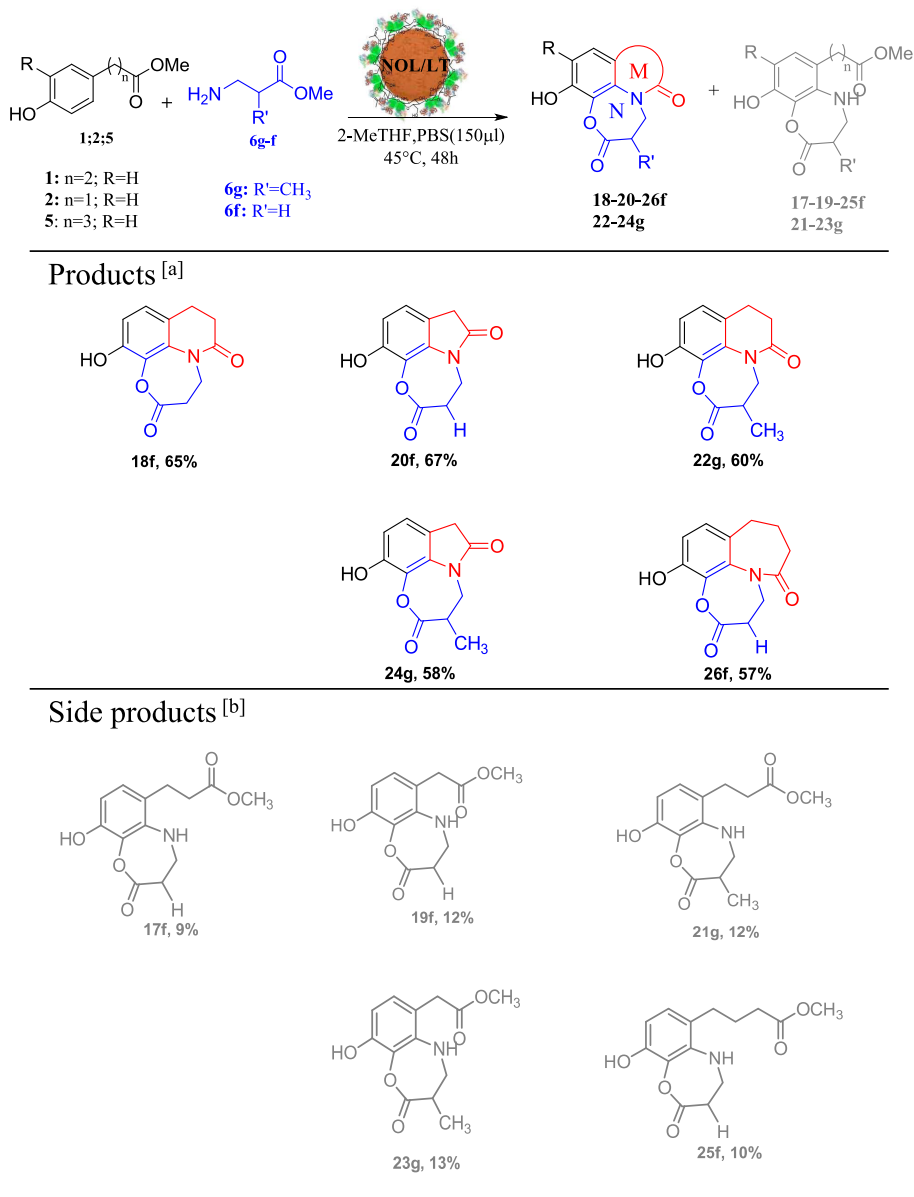
^aThe products yield was calculated on the basis of recovered product (mmol). Blue code: lactone ring. Red code: lactam ring. ^bYield at 12 h. ^cYield at 56 h. ^dYield in the presence of 400 μg of NOL/LT.

Table 2. Reusability of NOL/LT in the Synthesis of Tricyclic Benzoxazine 8a and Benzoxazepine 18f^a

runs	products	conversions [%]	yield [%]
1	8a [7a]	80	62 [12] ^b
2	8a [7a]	80	62 [11]
3	8a [7a]	78	59 [9]
4	8a [7a]	77	58 [8]
1	18f [17f]	78	65 [10]
2	18f [17f]	75	65 [12]
3	18f [17f]	75	62 [10]
4	18f [17f]	70	60 [9]

^aRuns were performed by recovering the catalyst at the end of the reaction, followed by washing with PBS. ^bYield in bracket is referred to side-products.

Reaction conditions for tricyclic 1,4-benzoxazines were first investigated in the synthesis of 8a from 1 and 6a as a selected case. The reaction was performed in 2-methyltetrahydrofuran (2-MeTHF) and limiting amount of PBS buffer, at 45 °C in an oil bath under dioxygen atmosphere (O₂) and in the presence of catalytic amount of NOL/LT for 48 h under gentle stirring. The amount of the catalyst (280 μg) was selected on the basis of previous data.² 2-MeTHF was selected as an environmentally friendly and low-polar solvent able to promote lipase activity.^{39,40} The small amount of PBS was crucial for tyrosinase hydration. The temperature of 45 °C was selected as optimal balance for the catalytic requirements of lipase in the multienzyme system.⁴¹ NOL/LT was removed and tricyclic 1,4-benzoxazine 8a (six-membered lactam ring) was obtained as the main reaction product, besides a low amount of bicyclic 1,4-benzoxazine 7a (Table 1). The reaction repeated under similar experimental conditions for 12 h afforded 8a in low yield. The

Table 3. Synthesis of Tricyclic 1,5-Benzoxazepine Derivatives and Related Side-Products

^aThe products yield was calculated on the basis of recovered product (mmol). Blue code: lactone ring. Red code: lactam ring.

yield of **8a** was not improved at 56 h (Table 1) or in the presence of a higher amount of NOL/LT (400 μ g), corresponding to an increase of 30% of the units of both enzymes. The optimal screening conditions for the synthesis of **8a** are summarized in Table S2. As reported in Scheme 2, the formation of **8a** required the 1,6-Michael addition of **6a** on quinone intermediate (diphenolase activity)^{12,42,43} to yield **1**, followed by tandem cascade of lactonization (compound **7a**) and lactamization (compound **8a**). Note that the formation of the oxazine ring was a consequence of the regioselectivity of the 1,6-Michael addition step.⁴⁴

The scope of the reaction was extended to α -amino acids methyl esters **6b–e** to analyze the chemical space of the lactone ring, providing **8b–e** in total good yields, besides a low amount of bicyclic **7b–e** (Table 1). Next, benzoxazines **10a–e** characterized by a 5-membered lactam ring were synthesized from methyl 2-(4-hydroxyphenyl)acetic acid **2** and **6a–e**, in the presence of a low amount of bicyclic **9a–e** (Table 1). The scaffold morphing was further improved to obtain an unsaturated lactam moiety by reaction of (*Z*)-3-(3,4-dihydroxyphenyl)acrylic acid **3** with **6a** to afford **12a** and **11a**. The lower yield of **12a** with respect to previously tricyclic derivatives was probably due to the formation of highly polar oxidative coupling compounds (not isolated in our case) involving the free catechol moiety of the substrate.⁴⁵ The 1 mmol scale synthesis of **8a** is reported in SI3 as a selected example. Spectroscopic data of compounds **7a–e**, **8a–e**, **9a–e**, **10a–e**, and **11–16a** are reported in SI4.

The reusability of NOL/LT was evaluated by recovering the catalyst at the end of the reaction (centrifugation, 15,000g for 10 min) followed by washing with PBS (pH 7.0, 0.1 M). NOL/LT retained the reactivity for at least 4 runs in the synthesis of **8a** as a selected example (Table 2; entries 1–4).

The reaction scope of the procedure was extended to the synthesis of tricyclic 1,5-benzoxazepine by using β -amino acid derivatives. Compound **1** and β -amino acids **6f** and **6g** (0.2 mmol) in 2-MeTHF (5.0 mL) and limiting amount of PBS buffer, were treated with catalytic amount of NOL/LT at 45 °C in an oil bath under dioxygen atmosphere (O₂) for 48 h. Under these experimental conditions, **18f** and **22f** (seven-membered ring lactone and six-membered ring lactam) were obtained as the main reaction products besides bicyclic **17f** and **21f** (Table 3). As an alternative, the reaction of **2** and β -amino acids **6f** and **6g** afforded **20f** and **24f** (seven-membered ring lactone and five-membered ring lactam) as the main reaction products besides bicyclic **19f** and **23f** (Table 3). In addition, the reaction of **5** and **6f** yielded **26f** (seven-membered ring lactone and seven-membered ring lactam) and **25f**, completing the selection of all possible combinatorial commutations for the closure of five-, six-, and seven-membered rings in the structure of the tricyclic molecule (Table 3). No appreciable differences were observed in the yield of benzoxazine between electron-donating OH and -donating OMe substituents. The effect of halogen-substituted groups was evaluated by analyzing the reaction between methyl 2-(3-bromo-4-hydroxyphenyl)acetate **6** and glycine **6a** as a selected case. 8-Bromo-9-hydroxy-[1,4]oxazino[2,3,4-*hi*]-indole-2,5(3*H*,6*H*)-dione **17a** was isolated in a yield (50%) comparable to that previously obtained for electron-donating substituent. Notably, electron-withdrawing substituents are reported to be deprived of specific effect on the ring closure of the benzoxazepine moiety.⁴⁶

The reusability of NOL/LT in the synthesis of **18f** was confirmed for at least 4 runs (Table 2; entries 5–8).

Spectroscopic data of compounds **18f–26f** are reported in SI5. Original ¹H NMR and ¹³C NMR spectra of novel tricyclic benzoxazine and benzoxazepine, and selected FT-IR spectra, are in SI6.

CONCLUSIONS

In summary, we demonstrated that an immobilized multi-enzyme cascade of lipase M and tyrosinase T may be successfully applied for the one-pot synthesis of tricyclic 1,4-benzoxazine and 1,5-benzoxazepine derivatives. The reaction proceeded under mild conditions, yielding the desired products from acceptable to high yield, with excellent atom economy and chemoselectivity. Both electron-donating groups and a bromine substituent were suitable for the transformation. Notably, the heterogeneous conditions significantly improved the sustainability of the reaction with respect to canonical multistep alternatives, limiting the production of wastes and reducing tedious purification steps. In addition, an 18-membered molecular library with diverse structural motifs was constructed, showcasing the efficiency of this approach starting from easily available starting compounds. Ongoing biological investigations will further explore the potential activity of these novel heterocycles.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.joc.4c02868>.

General experimental procedures; NOL/LT preparation and characterization; compound characterization data; and ¹H and ¹³C NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Authors

Elisabetta Tomaino – Department of Biological and Ecological Sciences, University of Tuscia, 01100 Viterbo, Italy;
Email: e.tomano@unitus.it

Raffaele Saladino – Department of Biological and Ecological Sciences, University of Tuscia, 01100 Viterbo, Italy;
orcid.org/0000-0002-4420-9063; Email: saladino@unitus.it

Authors

Eliana Capecchi – Department of Biological and Ecological Sciences, University of Tuscia, 01100 Viterbo, Italy;
orcid.org/0000-0002-5448-0658

Bruno M. Bizzarri – Department of Biological and Ecological Sciences, University of Tuscia, 01100 Viterbo, Italy;
orcid.org/0000-0001-7085-5432

Complete contact information is available at:

<https://pubs.acs.org/doi/10.1021/acs.joc.4c02868>

Author Contributions

[†]E.T. and B.M.B. contributed equally to this work. The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Safety Statement All reactions described in this work were carried out under standard laboratory conditions with commercially available reagents and solvents of low toxicity with no known significant risks under normal handling conditions. The products are chemically stable and do not pose significant environmental or health hazards based on available safety data.

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