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An electrochemical access to 2-amino-2,3-dihydro-1,4-benzodioxanes derived from hydroxytyrosol†

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The anodic oxidation of a natural antioxidative catechol, hydroxytyrosol, was developed in an acetonitrile/dimethylsulfoxide (or acetonitrile/water) solvent mixture to produce in a stable way the resulting non-activated *o*-quinone and generate structural analogues. 2-Amino-2,3-dihydro-1,4-benzodioxane derivatives were obtained as two regioisomers in good to high overall yields (65–90%) and 1 : 3 ratios, through an inverse electron demand Diels–Alder (IEDDA) reaction between the electrogenerated *o*-quinone and tertiary enamines. The insertion of an electron withdrawing (or electron donating) group on the catechol modified their relative proportions, so that the reaction became regiospecific. With some aliphatic enamines, a competitive 1,6-Michael addition took place, affording 2-hydroxy-1,2,4,5-tetrahydrobenzo[*d*]oxepine compounds.

Introduction

The Mediterranean diet induces various health benefits, in particular a lower incidence of cancers, diabetes, and cardiovascular and Alzheimer's diseases.[1] These effects attributed to the large consumption of fruits and vegetables are also correlated with the abundant intake of olives and extra virgin olive oil (EVOO), rich in fatty unsaturated acids and secoiridoids[2] such as oleuropein, ligstroside, oleacein and oleocanthal (Fig. 1).[3–5] Hydroxytyrosol **1**, a catechol compound present in high concentration in EVOO and constitutive of oleuropein aglycon, was found to contain strong radical scavenging properties as well as inhibiting activities on the inflammatory pathways.[6] Structural modifications have been carried out to improve its pharmacological properties.[7,8] Most of them consisted of the esterification of the alcohol chain with lipophilic acids[9] or protecting the catechol moiety responsible for the antioxidant properties with acetonide[10] or sulphate[11] groups. Other functionalisations of hydroxytyrosol **1** were realised on the 6-position of the aromatic ring, through nitration,[12] arylation[13] (Suzuki–Miyaura reaction), or cyclisation in isochroman[14] in the presence of carbonyl compounds.

During the past decades, the construction of 2,3-dihydro-1,4-benzodioxane rings from catechols was extensively developed, due to their occurrence in natural products and pharmaceutical compounds.[15] However, very few methods led to 2-amino-2,3-dihydro-1,4-benzodioxanes, although similar structures were identified in compounds isolated from insects[16–20] and marine organisms.[21] Such natural products isolated as pairs of two *trans* regioisomers, except in the case of orthidines A–D (Fig. 2), possess noticeable antioxidant and anti-inflammatory activities, including inhibition of cyclooxygenases. Therefore, we envisaged the synthesis of 2-amino-2,3-dihydro-1,4-benzodioxane derivatives starting from hydroxytyrosol **1**.

With the exception of a biomimetic oxidative dimerisation of *N*-acetyl-dehydrodopamine,[22] the principal route to 2-amino-2,3-dihydro-1,4-benzodioxanes consists of inverse electron-demand Diels–Alder reactions (IEDDA) between enamines and

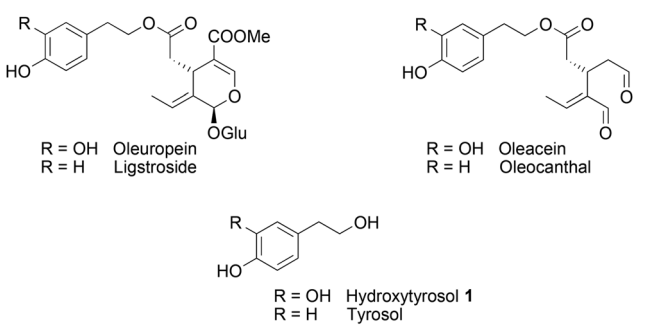

Fig. 1 Chemical structures of the major phenolic compounds in EVOO.

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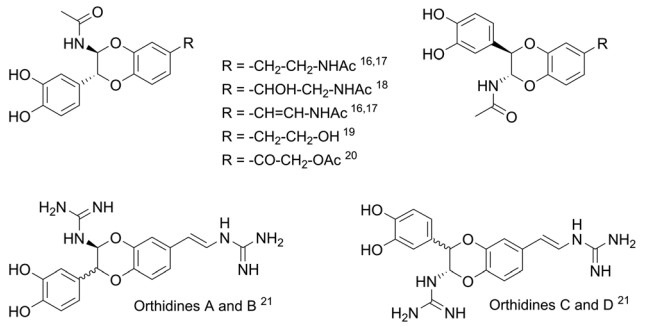
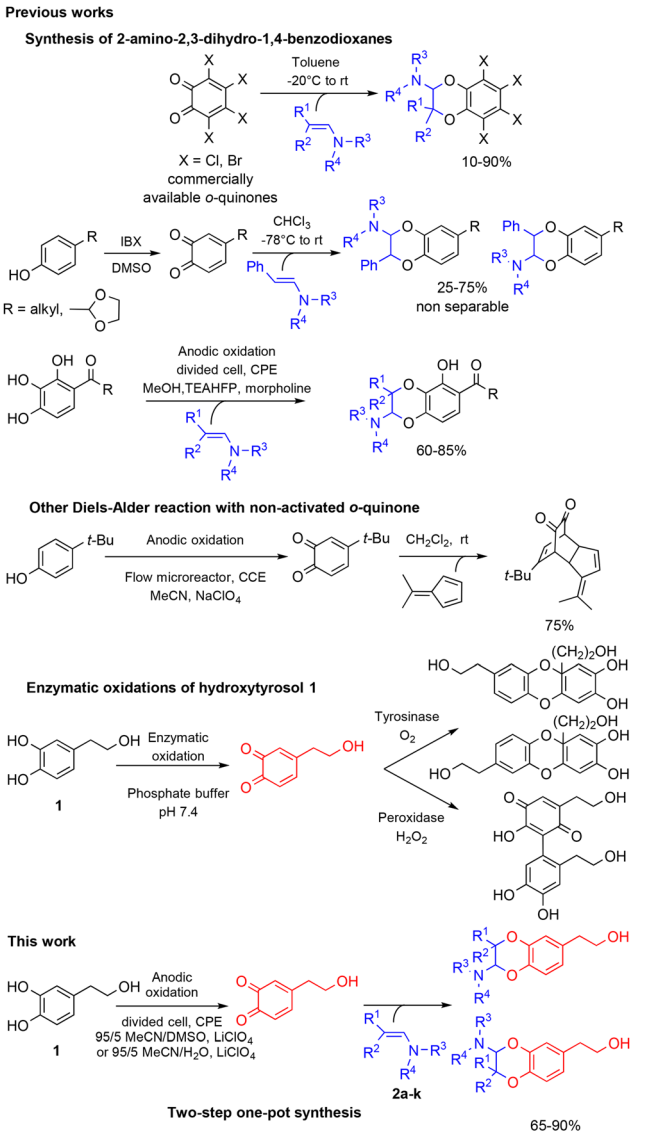


Fig. 2 Some natural 2-amino-2,3-dihydro-1,4-benzodioxanes.

o-quinone heterodienes. The *o*-quinones used then were commercially available halogenated *o*-quinones, such as *o*-chloranil and *o*-bromanil,[23] or *o*-quinones obtained through the oxidation of monophenols by IBX (Scheme 1).[24] A few years ago, we reported that the electrochemical oxidation of *o*-diphenols was an efficient tool for producing *o*-quinones under environmentally friendly conditions. These unstable species could be involved in further Michael reactions,[25,26] intramolecular cyclisation[27] or IEDDA reactions with enamines,[28] through diverse one-pot processes. Until now, [4 + 2] cycloadditions with enamine dienophiles were possible only from electron-poor electrogenerated *o*-quinone heterodienes (or electron-poor *o*-azaquinones).[29] Compared to the anodic oxidation of monophenols,[30] the electrochemical oxidation of non-activated catechols was less investigated, even if the resulting *o*-quinones engaged in subsequent reactions gave various compounds, such as catechol thioethers,[31,32] dihydroxy-phenyl-indolin-2-ones,[33] benzofurans,[34] or a dimethyl-fulvene coupling product.[35] Previously, two enzymatic oxidations of hydroxytyrosol **1** were attempted. None of them produced the expected *o*-quinone under stable conditions. The first led to a benzodioxan type dimer thanks to a catechol-quinone intermolecular 1,4-Michael addition,[36] while the second afforded, after the suroxidation of the transient *o*-quinone species, an hydroxylated quinonoid-phenyl dimer.[37]

Therefore, we describe herein an electrochemical process to generate in a stable way the expected *o*-quinone(s) and obtain, through an IEDDA reaction with enamines, 2-amino-2,3-dihydro-1,4-benzodioxanes derived from hydroxytyrosol **1**. The parameters that influence the [4 + 2] cycloaddition are further explored in terms of heterodienes (non-activated/activated electrogenerated *o*-quinones) and dienophiles (aromatic/aliphatic enamines).



Scheme 1 Reactivity of various *o*-quinone species.

Results and discussion

Synthesis of compounds 3 and 4

For this purpose, the solvent of the electrolysis had to be compatible both with the two-electron oxidation of the catechol and with the good stability of the enamine species involved in the [4 + 2] cycloaddition reaction. While the use of acetonitrile or dimethylformamide is usually preferred to generate radical intermediates such as phenoxyls, buffered aqueous solutions, methanol or water/acetonitrile solvent mixtures are often used for the oxidation of catechols into *o*-quinones. In aqueous buffered solutions, the pH of the solution and the concentration of the enamine strongly influence the rate of hydrolysis of the dienophile.[38] Therefore to start, a 50/50 (v/v) phosphate buffer pH 8.0/acetonitrile solvent was used for the electrochemical oxidation of hydroxytyrosol by controlled potential electrolysis. Under these conditions, the cyclic voltammogram of **1**, recorded at a platinum working electrode in the presence of 0.05 M $LiClO_4$ as the supporting electrolyte, showed a broad anodic peak Pa around +1.8 V *vs.* Ag/AgCl, without any cathodic peak on the reverse sweep (0.1 V s^{-1} scan rate). When the controlled potential of the electrolysis was fixed at +1.8 V *vs.* Ag/AgCl, a coulometric value of 2.0 ± 0.1 F was found for the number of electrons (n) involved in the oxidation of one mole of **1**. The monitoring of the UV-visible absorption spectrum in

the course of the electrolysis showed a decrease in the absorption band due to the neutral form of **1** at λ = 281 nm, while new bands developed at λ = 257 and 395 nm. The presence of four isosbestic points confirmed the existence of a simple equilibrium between the two species (Fig. 3), hydroxytyrosol **1** and the *o*-quinone species.

The addition of 1-(4-morpholino)-2,2-diphenylethene **2a** (5 equiv.) to the exhaustively oxidised solution induced the slow discolouration of the yellow colour characteristic of the *o*-quinone (30 min). Two 1,4-benzodioxane regioisomers **3** and **4**, separable by flash chromatography, could then be isolated in 61% overall yield, with 27/73 ratio (Table 1, entry 1).

The structural identification of the major regioisomer **4** was first established thanks to the HMBC correlation of the single hydrogen of the dihydrodioxin ring (δ_H = 5.70 ppm) with C-3 (Fig. S1†). As confirmed by X-ray crystallographic data (Fig. 4), the point of fixation of the morpholino group faced the 3-position. Comparatively, the hydrogen of the dihydrodioxin ring of the other 1,4-benzodioxane product correlated with C-4. Compound **3** was therefore identified as the second regioisomer that could be formed through the [4 + 2] cycloaddition between the enamine and the electrogenerated *o*-quinone (see the equation in Table 1).

Optimisation of reaction conditions

Usually, the yields of the IEDDA reactions markedly depend on the nature of the solvent.[39] Here, the replacement of 50/50 water/acetonitrile solvent with pure acetonitrile or methanol induced strong modifications in the evolution of UV-visible spectra, together with the loss of isosbestic points (Table 1, entries 2–4). No formation of stable o-quinone was possible, whatever the ionisation level under which the hydroxytyrosol catechol was oxidised: neutral species (entry 3) or monoanionic form obtained through morpholine addition (entry 4).[28]

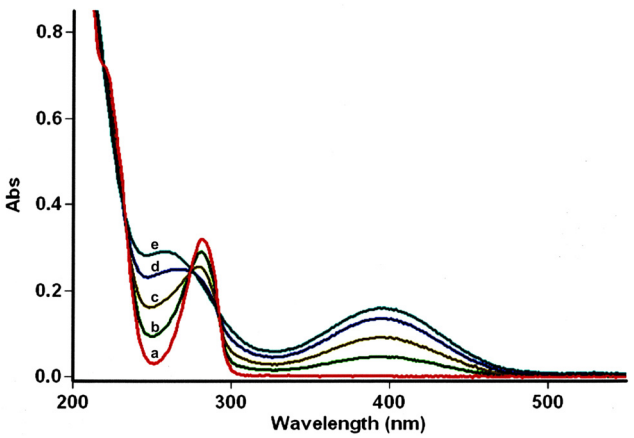
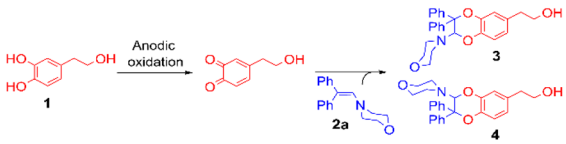


Fig. 3 UV-visible absorption spectra in the course of the anodic oxidation of **1**. Hydroxytyrosol **1** (1.25 mM), 50/50 (v/v) phosphate buffer pH 8.0/acetonitrile solution containing $LiClO_4$ (0.05 M) as the supporting electrolyte, platinum anode, E_{ox} = +1.8 V *vs.* Ag/AgCl, stirring for 40 min under Ar at room temperature. (a) Before electrolysis, (b) 0.5 F mol^{-1}, (c) 1.0 F mol^{-1}, (d) 1.5 F mol^{-1}, and (e) 2.0 F mol^{-1}.

Table 1 Optimisation of the two-step one-pot reaction conditions[a,b]



Entry	Solvent	Potential	Equiv. of enamine	Yield[c]	Ratio[d] 3/4
1	50/50 H_2O/MeCN[e]	+1.8 V	5	61%	27/73
2	MeCN	+1.4 V	5	—	—
3	MeOH[f]	+1.0 V	5	—	—
4	MeOH[f,g]	+1.0 V	5	—	—
5	95/5 MeCN/DMSO	+1.0 V	5	71%	24/76
6	95/5 MeCN/DMSO	+1.0 V	2.5	90%	24/76
7	95/5 MeCN/DMSO	+1.0 V.	1.2	90%	25/75
8	95/5 MeCN/H_2O	+1.0 V	5	63%	24/76
9	95/5 MeCN/H_2O	+1.0 V	1.2	27%	24/76

[a] Electrosynthesis: [**1**] = 1.25 mM, 0.05 M $LiClO_4$ as the supporting electrolyte, divided cell, platinum grid anode, platinum plate cathode,[40] oxidation potential E_{ox} referred to Ag/AgCl. [b] Diels–Alder reaction: addition of enamine **2a** to a solution of *o*-quinone. [c] Overall isolated yield of both regioisomers **3** and **4**. [d] ^{1}H NMR ratio of **3**/**4**. [e] Aqueous phase = 3 mM phosphate buffer pH 8.0. [f] 0.05 M $LiClO_4$ replaced with 0.02 M NEt_4PF_6. [g] +5 equiv. of morpholine.

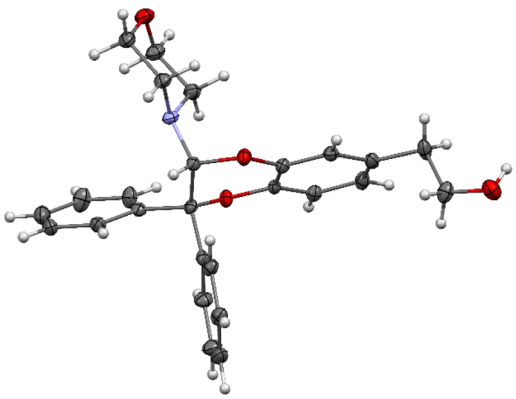


Fig. 4 ORTEP view of compound **4**. Displacement ellipsoids are drawn at the 50% probability level.

To limit the hydrolysis of enamine without affecting the rate of the cycloaddition, we replaced the large amount of water (50% of aqueous buffer pH 8.0) with 5% of dimethylsulfoxide. The potential of the platinum anode could then be fixed at a lower potential (+1.0 V *vs.* Ag/AgCl), since the cyclic voltammogram exhibited an anodic peak at +0.9 V *vs.* Ag/AgCl (scan rate 0.1 V s^{-1}). A small cathodic peak appeared on the reverse sweep at 0 V. *vs.* Ag/AgCl corresponding to the reduction of the electrogenerated *o*-quinone (Fig. S2†). As previously observed in the water/acetonitrile solvent, a coulometric value of 2.0 ± 0.1 F was necessary for the exhaustive oxidation of one mole of hydroxytyrosol **1**. Under these optimised reaction conditions, the yield of **3** and **4** reached 90%, even in the presence of only 1.2 equiv. of enamine (entries 5–7).

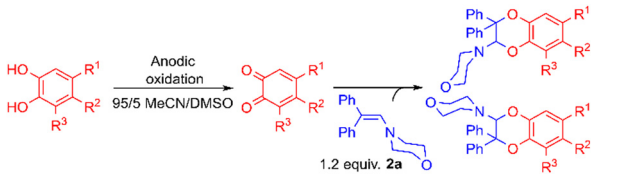
The reaction efficiency was still suitable in 95/5 acetonitrile/water mixtures with 5 equiv. of enamine (entry 8), with the ratio of regioisomers **3** and **4** remaining close to 25/75. However, decreasing the amount of enamine to 1.2 equiv. was no more possible without a severe diminution of the yield (entry 9).

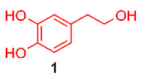
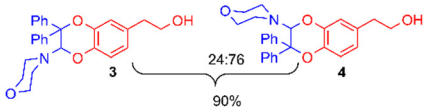
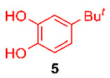
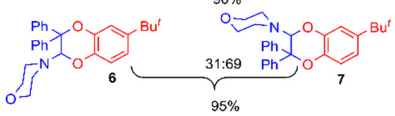
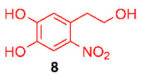
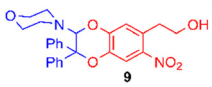
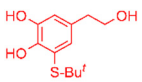
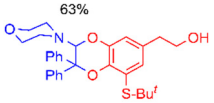
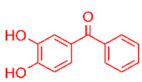
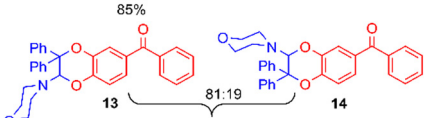
The importance of the order of addition of the diene and the dienophile should be underlined. The dienophile (enamine) had to be added to the diene solution (*o*-quinone). When MeCN/water solution of *o*-quinone was added in fractions to MeCN solution of 5 equiv. of enamine, no 1,4-benzodioxane formed. In the presence of water, the partial hydrolysis of the enamine induced the liberation of an excess of base (morpholine) and the polymerisation of a small fraction of *o*-quinone (dark purple colour).

Variation of the catechol substrate and ratio of the regioisomers

Using the conditions providing the best yield with enamine **2a** (95/5 MeCN/DMSO, 1.2 equiv. of enamine), we turned to other catechol substrates to evaluate the regioselectivity of the [4 + 2] cycloaddition (Table 2). With 4-*tert*-butyl-catechol **5**, another source of non-activated *o*-quinone, two regioisomers **6** and **7** could be synthesised in 95% overall yield. As expected for an IEDDA reaction, in the presence of compound **8**, for the hydroxytyrosol homologue bearing an electron-withdrawing nitro group in position 6, compound **9** was the sole regioisomer formed (63% yield). With compound **10** substituted in position 5 by the –S-*tBu* hindered thiol group, the reaction afforded also only one regioisomer **11** (85% yield). In contrast, with 3,4-dihydroxybenzophenone **12**, bearing an electron-withdrawing group in position 1, the concerted attack of the enamine is favoured on the oxo in position 3, leading to compounds **13**/**14** in 81/19 ratio and 71% overall yield.

Table 2 Regioselectivity of the reaction depending on the substrates[a,b]



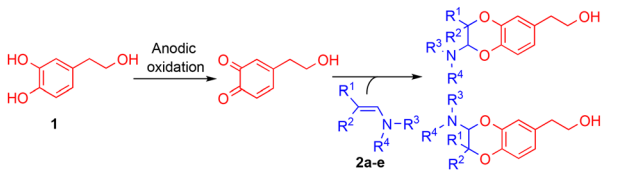
Catechol	2-Amino-2,3-dihydro-1,4-benzodioxanes[c]
 1	 3 / 4 — 24:76 — 90%
 5	 6 / 7 — 31:69 — 95%
 8	 9 — 63%
 10	 11 — 85%
 12	 13 / 14 — 81:19 — 71%

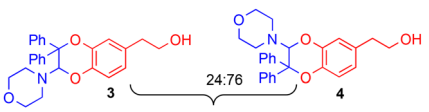
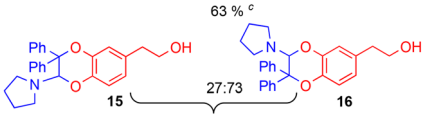
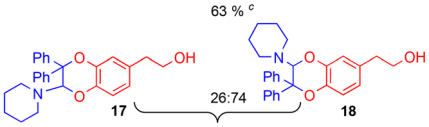
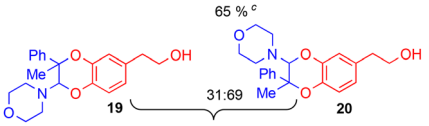
[a] Electrosynthesis: [catechol] = 1.25 mM, [$LiClO_4$] = 0.05 M, divided cell, platinum grid anode, platinum plate cathode, E_{ox} = +1.4 V *vs.* Ag/AgCl (except for compound **1**, E_{ox} = +1.0 V *vs.* Ag/AgCl), 95/5 MeCN/DMSO. [b] Diels–Alder reaction: addition of 1.2 equiv. of enamine **2a** to a solution of *o*-quinone. [c] Isolated yields of regioisomers separable by flash chromatography (except for regioisomer **14**).

Variation of the dienophile part

Aromatic enamines. We tried in the second step to extend the reaction to other tertiary aromatic enamines previously synthesised. The replacement of the morpholine group with the pyrrolidine or piperidine group (Table 3), was correlated

Table 3 Reaction with aromatic enamines[a]



Enamine	2-Amino-2,3-dihydro-1,4-benzodioxanes[d]
 2a	 3 / 4 — 24:76 — 90 %[b] 63 %[c]
 2b	 15 / 16 — 27:73 — 74 %[b] 63 %[c]
 2c	 17 / 18 — 26:74 — 65 %[b] 65 %[c]
 2d	 19 / 20 — 31:69 — 41 %[b] 79 %[c]
 2e	—

[a] [Catechol] = 1.25 mM, [$LiClO_4$] = 0.05 M, divided cell, platinum grid anode, platinum plate cathode, E_{ox} = + 1.0 V *vs.* Ag/AgCl. Solvent of electrolysis and quantity of enamine added for the Diels–Alder reaction: [b] 95/5 MeCN/DMSO, 1.2 equiv. of enamine. [c] 95/5 MeCN/H_2O, 5 equiv. of enamine. [d] Isolated yields of regioisomers separable by flash chromatography.

with a decrease in the yield from 90% to 65–74%, consistent with an increase of the pK_a of the amine arising from the partial hydrolysis of the enamine. When 95/5 MeCN/DMSO solvent (1.2 equiv. of enamine) was changed to a 95/5 MeCN/H_2O mixture (5 equiv. enamine), the yields became nearly equal to 64%, independently of the amine. The rates of hydrolysis of enamines **2a–2c** derived from 2,2-diphenylacetaldehyde (R^1 = R^2 = Ph) were probably very similar, as observed with enamines derived from 2-methylpropionanaldehyde (R^1 = R^2 = Me) in pH 5.0 buffered aqueous solutions.[38b]

The improving impact of water on Diels–Alder reactions usually reported[41] appeared more clearly with the enamine **2d** (R^1 = Ph, R^2 = Me), since the yield almost doubled from 41% to 79%, with 5% of water instead of 5% of DMSO. However, no stable product could be isolated with secondary enamine **2e** (R^1 = Ph, R^2 = H), whatever the solvent mixture used.

Since the enamine **2d** had different substituents R^1 = Ph and R^2 = Me, regioisomers **19** and **20** were obtained as two pairs of diastereoisomers **19′**,**19″** and **20′**,**20″**, in 18.5:12/44.5:25 ratio (Fig. 5). In the case of compounds **20′** and **20″**, the proton of the dihydrodioxin ring H_{dioxin}-**20′** was located at 5.02 ppm while H_{dioxin}-**20″** was located at 4.88 ppm. Both of them presented an HMBC correlation with C-3. NOESY experiments revealed that the methyl group of **20′** was on the same face as CH_2-O and CH_2-N of the morpholine group. Comparatively, in compound **20″** the morpholine faced the phenyl and methylene CH_2-N correlating with aromatic protons. In the same way, HMBC and NOESY correlations showed that compound **19′** resulted from the *trans* coupling mode, with compound **19″** corresponding to the *cis* one. The ^{1}H NMR spectral evolution of a 6.25 × 10^{-3} M solution of crystallised *trans* enamine **2d**[42] in 95/5 CD_3CN/D_2O confirmed that no isomerisation of the dienophile occurred under these conditions.

Aliphatic enamines. When the reaction was conducted in the presence of aliphatic enamines **2f–2h**, the 95/5 MeCN/H_2O mixture of solvents offered the best results, accelerating the cycloaddition against the enamine hydrolysis, facilitated by the absence of conjugated aromatic rings. The 2-amino-2,3-dihydro-1,4-benzodioxins **21–26** were obtained in good yields (Table 4, entries 1–3). Surprisingly, the replacement of the morpholine group with piperidine or pyrrolidine had an increasing effect on the yields, correlated with the enhancement of the electron donating effect of the enamine substituents.

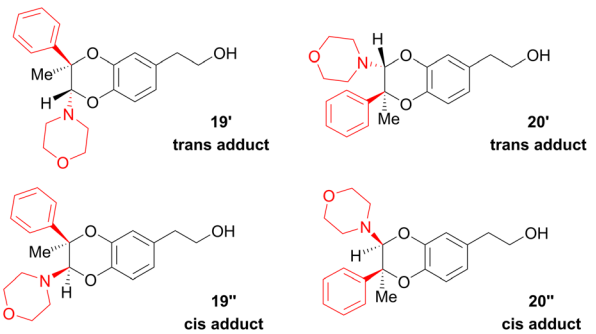
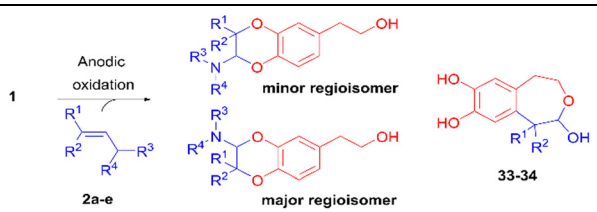


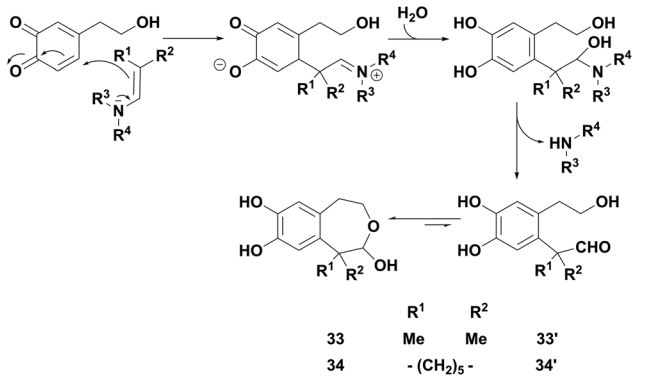
Fig. 5 Relative configuration of the four regioisomeric products **19′**,**19″**/**20′**,**20″** obtained through the IEDDA reaction between the *o*-quinone and enamine **2d**.

Table 4 Reaction with aliphatic enamines[a]



Entry		Enamine R^1	R^2	HN (R^3,R^4)	Benzodioxanes	Yield[b]	Benzoxepine	Yield
1	**2f**	Et	Et		**21**/**22**	65%	—	—
2	**2g**	Et	Et		**23**/**24**	87%	—	—
3	**2h**	Et	Et		**25**/**26**	85%	—	—
4	**2i**	Et	Et		**27**/**28**	26%	**33**	18%
5	**2j**	Me	Me		**29**/**30**	41%	**33**	41%
6	**2k**	Cyclohexyl			**31**/**32**	27%	**34**	49%

[a] Conditions of electrosynthesis: [catechol] = 1.25 mM, divided cell, platinum grid anode, platinum plate cathode, E_{ox} = + 1.0 V *vs.* Ag/AgCl, [$LiClO_4$] = 0.05 M, 95/5 MeCN/H_2O, 5 equiv. of extemporaneously prepared enamine. [b] Overall yield after flash chromatography, **21**/**22** separable by HPLC.



Scheme 2 Proposed mechanism for the formation of 1,2,4,5-tetrahydrobenzo[*d*]oxepines **33** and **34**.

With enamines bearing methyl or cyclohexyl groups, a competitive reaction occurred which generated original 1,2,4,5-tetrahydrobenzo[*d*]oxepines **33** and **34** (entries 4–6). Such compounds, hydroxylated in the 2-position, were in solution in equilibrium with their aldehyde open forms **33′** and **34′**, as characterised by the ^{1}H NMR spectrum in acetone-d^6. They probably resulted from a 1,6-Michael addition of the enamine on the electrogenerated *o*-quinone (Scheme 2), followed, in the presence of water, first by the elimination of the amine and then by the intramolecular cyclisation of the resulting transient aldehyde. In the specific case of hindered enamine **2k**, this reaction became predominant, so that compound **34** was isolated as the major product in 49% yield.

Conclusion

In summary, we have developed an electrochemical method to modify the catechol moiety of hydroxytyrosol **1** (or analogues) and obtained 2-amino-2,3-dihydro-1,4-benzodioxane derivatives, through the cycloaddition of enamines with the corresponding *o*-quinone(s). The use of the 95/5 MeCN/DMSO (or 95/5 MeCN/H_2O) mixture as the solvent, combined with the anodic oxidation of hydroxytyrosol under the neutral form, turned out to be compatible both with the bi-electronic oxidation of the catechol into *o*-quinone and with the enamine cycloaddition. As expected, the regiospecificity of the reaction is determined by the presence of electron-withdrawing (or electron-donating) substituents on the *o*-quinone, favouring the cycloaddition of the enamine on one of the other oxo groups of the diene. With non-activated *o*-quinone, two regioisomers were obtained, whose substituents in the 3-position of the 1,4-benzodioxin ring could be aromatic or aliphatic. Our objective in the future will be to apply this method to other catechols abundant in olive oil, such as oleuropein.

Conflicts of interest

There are no conflicts to declare.

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References

1 (*a*) M. Guasch-Ferré and W. C. Willett, *J. Intern. Med.*, 2021, **290**, 549; (*b*) R. J. Widmer, A. J. Flammer, L. O. Lerman and A. Lerman, *Am. J. Med.*, 2015, **128**, 229.
2 (*a*) H. Lemoine, D. Marković and B. Deguin, *J. Org. Chem.*, 2014, **79**, 4358; (*b*) K. Vougogiannopoulou, C. Lemus, M. Halabalaki, C. Pergola, O. Werz, A. B. Smith III, S. Michel, L. Skaltsounis and B. Deguin, *J. Nat. Prod.*, 2014, **77**, 441.
3 S. Charoenprasert and A. Mitchell, *J. Agric. Food Chem.*, 2012, **60**, 7081.
4 V. Francisco, C. Ruiz-Fernández, V. Lahera, F. Lago, J. Pino, L. Skaltsounis, M. A. González-Gay, A. Mobasheri, R. Gómez, M. Scotece and O. Gualillo, *J. Agric. Food Chem.*, 2019, **67**, 3845.
5 A. Angelis, D. Michailidis, L. Antoniadi, P. Stathopoulos, V. Tsantila, J.-M. Nuzillard, J.-H. Renault and L. A. Skaltsounis, *Sep. Purif. Technol.*, 2021, **255**, 117692.
6 T. Hu, X.-W. He, J.-G. Jiang and X.-L. Xu, *J. Agric. Food Chem.*, 2014, **62**, 1449.
7 M. Oliverio, M. Nardi, M. L. Di Gioia, P. Costanzo, S. Bonacci, S. Mancuso and A. Procopio, *Nat. Prod. Rep.*, 2021, **38**, 444.
8 A. Procopio, S. Alcaro, M. Nardi, M. Oliverio, F. Ortuso, P. Sacchetta, D. Pieragostino and G. Sindona, *J. Agric. Food Chem.*, 2009, **57**, 11161.
9 (*a*) M. Trujillo, R. Mateos, L. Collantes de Teran, J. L. Espartero, R. Cert, M. Jover, F. Alcudia, J. Bautista, A. Cert and J. Parrado, *J. Agric. Food Chem.*, 2006, **54**, 3779; (*b*) A. Procopio, C. Celia, M. Nardi, M. Oliverio, D. Paolino and G. Sindona, *J. Nat. Prod.*, 2011, **74**, 2377.
10 A. Gambacorta, D. Tofani, R. Bernini and A. Migliorini, *J. Agric. Food Chem.*, 2007, **55**, 3386.
11 P. Begines, D. Biedermann, K. Valentová, L. Petrásková, H. Pelantová, I. Maya, J. G. Fernández-Bolaños and V. Křen, *J. Agric. Food Chem.*, 2019, **67**, 7281.
12 M. Trujillo, E. Gallardo, A. Madrona, L. Bravo, B. Sarriá, J. A. González-Correa, R. Mateos and J. L. Espartero, *J. Agric. Food Chem.*, 2014, **62**, 10297.
13 R. Bernini, S. Cacchi, G. Fabrizi and E. Filisti, *Org. Lett.*, 2008, **10**, 3457.
14 M. Guiso, C. Marra and C. Cavarischia, *Tetrahedron Lett.*, 2001, **42**, 6531.
15 For examples, see: (*a*) S. F. Campbell, M. J. Davey, J. D. Hardstone, B. N. Lewis and M. J. Palmer, *J. Med. Chem.*, 1987, **30**, 49; (*b*) Y. Liu and W. Bao, *Org. Biomol.*

Chem., 2010, **10**, 2700; (*c*) J. Habermann, S. V. Ley, J. J. Scicinski, J. S. Scott, R. Smits and A. W. Thomas, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2425; (*d*) M. Massacret, P. Lhoste, R. Lakhmiri, T. Parella and D. Sinou, *Eur. J. Org. Chem.*, 1999, 2665; (*e*) N. R. Guz and F. R. Stermitz, *J. Nat. Prod.*, 2000, **63**, 1140; (*f*) T. Song, B. Zhou, G.-W. Peng, Q.-B. Zhang, L.-Z. Wu, Q. Liu and Y. Wang, *Chem. – Eur. J.*, 2014, **20**, 678; (*g*) K. C. Nicolaou, J. Wang and Y. Tang, *Angew. Chem., Int. Ed.*, 2008, **47**, 1432.

16 Y.-N. Shi, Z.-C. Tu, X.-L. Wang, Y.-M. Yan, P. Fang, Z.-L. Zuo, B. Hou, T.-H. Yang and Y.-X. Cheng, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 5164.

17 Y.-M. Yan, L.-J. Li, X.-C. Qin, Q. Lu, Z.-C. Tu and Y.-X. Cheng, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 2469.

18 L. Yang, G. Y. Li, H. Y. Wang, K. Zhang, Y. Zhu, W. Zhao, H. Wang and J. H. Wang, *Phytochem. Lett.*, 2016, **16**, 97.

19 X.-Q. Pang, X.-M. Wu, Q. Wang, D. Meng, Y.-M. Huang, J.-L. Xu, Y. Li, H. Liu, H. Xiao and Z.-T. Ding, *Nat. Prod. Commun.*, 2022, **17**, 1.

20 P. Thapa, Y. Gu, Y.-S. Kil, S. C. Baek, K. H. Kim, A.-R. Han, E. K. Seo, H. Choi, J.-H. Chang and J.-W. Nam, *Bioorg. Chem.*, 2020, **102**, 104095.

21 A. N. Pearce, E. W. Chia, M. V. Berridge, E. W. Maas, M. J. Page, J. L. Harper, V. L. Webb and B. R. Copp, *Tetrahedron*, 2008, **64**, 5748.

22 Y. S. Cheah, S. Santhanakrishnan, M. B. Sullivan, K. G. Neoh and C. L. L. Chai, *Tetrahedron*, 2016, **72**, 6543.

23 W. Ried and E. Torok, *Justus Liebigs Ann. Chem.*, 1965, 187.

24 J. Zhang, C. Taylo, E. Bowman, L. Savage-Low, M. W. Lodewyk, L. Hanne and G. Wu, *Tetrahedron Lett.*, 2013, **54**, 6298.

25 C.-M. Martinez, A. Neudörffer and M. Largeron, *Org. Biomol. Chem.*, 2012, **10**, 3739.

26 A. Felim, A. Urios, A. Neudörffer, G. Herrera, M. Blanco and M. Largeron, *Chem. Res. Toxicol.*, 2007, **20**, 685.

27 K. Cottet, A. Neudörffer, M. Kritsanida, S. Michel, M.-C. Lallemand and M. Largeron, *J. Nat. Prod.*, 2015, **78**, 2136.

28 D. Xu, A. Chiaroni and M. Largeron, *Org. Lett.*, 2005, **7**, 5273.

29 M. Largeron, A. Neudorffer, M. Vuilhorgne, E. Blattes and M.-B. Fleury, *Angew. Chem., Int. Ed.*, 2002, **41**, 824.

30 (*a*) S. Yamamura and S. Nishiyama, *Synlett*, 2002, 533; (*b*) T. Yamamoto, T. Saitoh, Y. Einaga and S. Nishiyama, *Chem. Rec.*, 2021, **21**, 1; (*c*) S. R. Waldvogel and B. Janza, *Angew. Chem., Int. Ed.*, 2014, **53**, 7122; (*d*) B. Elsler, D. Schollmeyer and S. R. Waldvogel, *Faraday Discuss.*, 2014, **172**, 413.

31 D. Nematollahi and E. Tammari, *J. Org. Chem.*, 2005, **70**, 7769.

32 C.-C. Zeng, D.-W. Ping, S.-C. Zhang, R.-G. Zhong and J. Y. Becker, *J. Electroanal. Chem.*, 2008, **622**, 90.

33 D. Nematollahi, S. S. H. Davarani and P. Mirahmad, *ACS Sustainable Chem. Eng.*, 2014, **2**, 579.

34 D. Nematollahi, D. Habibi, M. Rahmati and M. Rafiee, *J. Org. Chem.*, 2004, **69**, 2637.

35 K. Tanaka, H. Yoshizawa and M. Atobe, *Synlett*, 2019, **30**, 1194.

36 D. Vogna, A. Pezzella, L. Panzella, A. Napolitano and M. d'Ischia, *Tetrahedron Lett.*, 2003, **44**, 8289.

37 M. De Lucia, L. Panzella, A. Pezzella, A. Napolitano and M. d'Ischia, *Tetrahedron*, 2006, **62**, 1273.

38 (*a*) P. Y. Sollenberger and R. B. Martin, *J. Am. Chem. Soc.*, 1970, **92**, 4261; (*b*) W. Maas, M. J. Janssen, E. J. Stamhuis and H. Wynberg, *J. Org. Chem.*, 1967, **32**, 1111.

39 C. Cativiela, J. I. Garcia, J. A. Mayoral and L. Salvatella, *Chem. Soc. Rev.*, 1996, 209.

40 Similar results were obtained when replacing in entry 1 $LiClO_4$ with NaCl or in entry 2 $LiClO_4$ with TEAHFP. The platinum anode could be replaced with carbon graphite, and the platinum cathode with carbon felt (Table S1†).

41 A. Kumar, *Chem. Rev.*, 2001, **101**, 1.

42 L. Duhamel, P. Duhamel, S. Combrisson and P. Siret, *Tetrahedron Lett.*, 1972, **34**, 3603.