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$Zn(OTf)_2$-Catalyzed 1,6-Conjugate Addition of Benzoxazinones to *p*-Quinone Methides: Access to 3,3-Diaryl-2-(2-oxo-2*H*-1,4-benzoxazin-3-yl)propanoic Acid Esters

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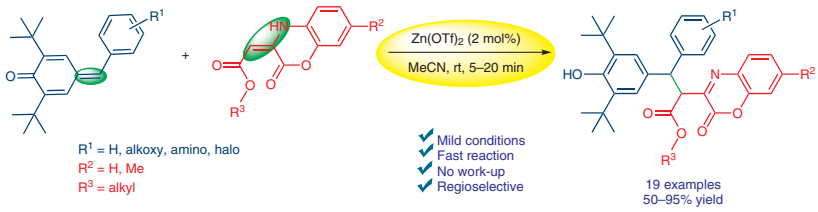

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Abstract An effective method for the synthesis of 3,3-diaryl-2-(2-oxo-2*H*-1,4-benzoxazin-3-yl)propanoic acid esters is reported. A novel zinc triflate-catalyzed regioselective 1,6-conjugate addition of vinylogous carbamates to *p*-quinone methides for accessing the title compounds has been developed. This protocol furnished the hybrid compounds in good to excellent yields. The reaction is rapid and has a broad substrate scope.

Key words *para*-quinone methides, vinylogous carbamates, 1,6-addition, regioselectivity, diastereoselectivity, benzoxazines

Carbon–carbon bond formation is a ubiquitous process in organic synthesis, and the C–C bond is the most common and adaptable bond in nature.[1] The development of highly efficient strategies to construct C–C bonds in organic synthesis is a challenging task. C–C bond formation in organic molecules is a powerful tool for the construction of natural products and industrial applications.[2] It also has an extensive range of applications, for example in the production of medicinal and pharmaceutical agents.[3,4] Diverse methodologies for C–C bond formation in a range of molecules have been established, such as base-catalyzed enolate chemistry by providing an alkyl partner attached to the α-position of carbonyl compounds,[5] palladium-catalyzed C-3 arylation,[6] alkynylation,[7] acylation,[8] carbonylation, and reactions under metal-free conditions.[9] Gardner et al. reported the reaction of *o*-quinone methides with sodium cyanide and diethyl malonate under basic conditions to induce C–C bond formation.[10]

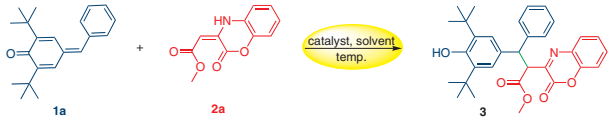
It is established that hybrid compounds possess multiple biological and pharmacological properties.[11] The assimilation of vinylogous carbamates into a diarylmethide moiety should provide a good possibility of discovering some novel bioactive molecules. In recent years, *para*-quinone methides (*p*-QMs) have attracted a great deal of attention from the synthetic community due to their exclusive reactivity and their capacity to form the complex architectures found in various pharmaceutical and natural products.[12,13] *p*-QMs have been extensively used in carbon–carbon and carbon–heteroatom bond formation processes through nucleophilic addition because of the stability acquired through their aromatization during the conjugate addition reaction.[14] In fact, the 1,6-conjugate addition of nucleophilic reagents to *p*-QMs is a challenging task, as it can proceed by 1,2- and 1,4-additions, along with 1,6-addition. Various parameters that affect the regioselectivity of conjugate addition include the choice of catalyst, the nature of the nucleophile reagent, and the structure of the Michael acceptor.[15] A classical reaction of *p*-QMs involves rearomatization through nucleophilic addition of a variety of carbon, sulfur, nitrogen, oxygen, or phosphorus nucleophiles through 1,6-conjugate addition. Anand and co-workers targeted the synthesis of α-arylated nitriles and α,α-diarylated ketones by using N-heterocyclic carbenes.[16] Li and co-workers reported the synthesis of a organophosphorus compounds[17] and a β-bisaryl amide[18] through base-catalyzed 1,6-conjugate additions to *p*-QMs. The Muthukrishnan group synthesized α-arylated nitriles by $BF_3{\cdot}Et_2O$-catalyzed cyanation of a *p*-QM by using *tert*-butyl isocyanide.[19] Thus 1,6-conjugate addition of reactive *p*-quinone methide synthons is an important technique for the generation of functionalized diarylmethanes.[20]

In the area of heterocyclic chemistry, benzoheterocyclic motifs and their derivatives have found biological,[21] pharmacological,[22] and agrochemical applications.[23] Among benzoheterocycles, 1,4-benzoxazine derivatives have attracted considerable attention because they exhibit a wide range of biological activities, for example as antagonists,[24] antibacterial agents,[25] or antipsychotic agents.[26] In view of

their high reactivity and efficiency, the development of new reacting partners would be keenly anticipated. Inspired by the advantages of these motifs, it occurred to us that Lewis acid-catalyzed 1,6-conjugate addition of benzoxazinones to *p*-quinone methides might give access to functionalized vinylogous carbamates.

As a prelude to achieving this objective, the *p*-quinone methide **1a** and the vinylogous carbamate **2a** were chosen as model substrates, and an initial reaction was conducted between them in the presence of 5 mol% zirconium(IV) chloride as a catalyst in dichloromethane at room temperature. Gratifyingly, the expected product **3** was isolated in 35% yield after 18 hours (Table 1, entry 1). Encouraged by this initial result, we next screened various Lewis acid catalysts [$SnCl_2{\cdot}2H_2O$, $AlCl_3$, $ZnCl_2$ $FeCl_3$, I_2, $Zn(OTf)_2$, and $Cu(OTf)_2$] (entries 2–8) and Brønsted acid catalysts (*p*-toluenesulfonic acid, trifluoroacetic acid, and polyphosphoric acid) (entries 9–11) to identify the best catalyst for this transformation. Among the above Lewis acid and Brønsted acid catalysts, $Zn(OTf)_2$ was found to be the most effective, giving the desired product **3** in 70% yield (entry 7). The reaction was further examined by switching to various polar protic, nonpolar protic, or halogenated solvents [ethyl acetate, ethanol, methanol, DMF, toluene, chloroform, dichloroethane, and acetonitrile] (entries 12–17), and the results revealed that acetonitrile was superior to the other solvents (entry 17). Next, we examined the effect of the catalyst loading by changing the amount of catalyst from 2 to 20 mol% (entries 18–20). There was no significant change in the yield of product **3**, and therefore 2 mol% of $Zn(OTf)_2$ in appeared ideal for this reaction, as it provided the product in 93% yield (entry 20). However, the reaction of **1a** with **2a** displayed a low diastereoselectivity that was not significantly improved on screening various solvents, Lewis and

Table 1 Optimization of Conditions for the 1,6-Conjugate Addition of a Benzoxazine with a *p*-Quinone Methide[a]

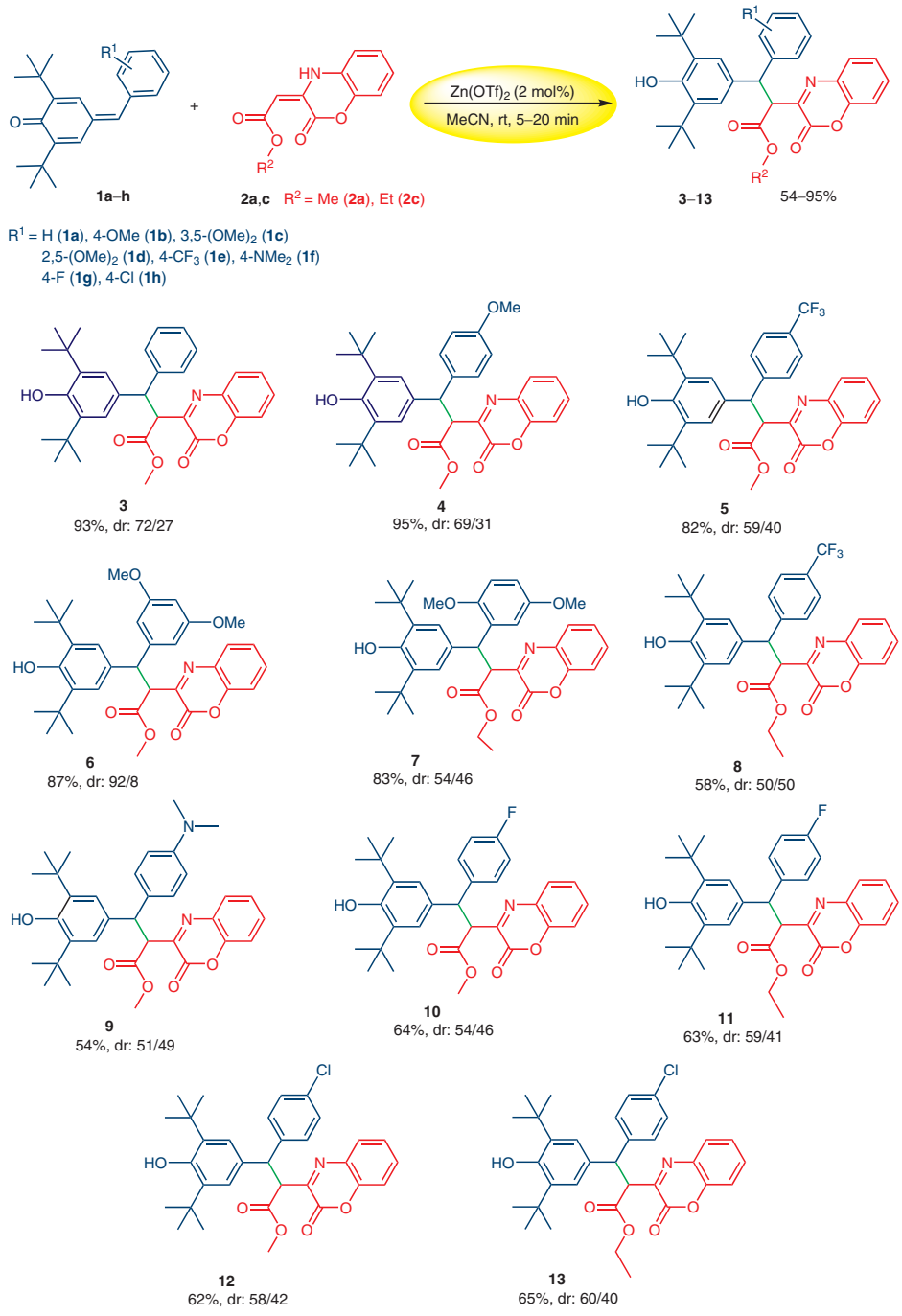


Entry	Acid (mol%)	Solvent	Temp (°C)	Time	Yield (%)	dr[b]
1	$ZrCl_4$ (5)	CH_2Cl_2	rt	18 h	35	44:66
2	$SnCl_2{\cdot}2H_2O$ (5)	CH_2Cl_2	rt	18 h	33	46:54
3	$AlCl_3$ (5)	CH_2Cl_2	rt	18 h	nr[d]	–
4	$ZnCl_2$ (5)	CH_2Cl_2	rt	18 h	50	52:48
5	$FeCl_3$ (5)	CH_2Cl_2	rt	18 h	nr	–
6	I_2 (5)	CH_2Cl_2	rt	18 h	30	47:53
7	$Zn(OTf)_2$ (5)	CH_2Cl_2	rt	18 h	70	72:27
8	$Cu(OTf)_2$ (5)	CH_2Cl_2	rt	18 h	traces	–
9	TSA (5)	CH_2Cl_2	rt	5 min	29	47:53
10	TFA (5)	CH_2Cl_2	rt	18 h	34	46:54
11	PPA (5)	CH_2Cl_2	rt	10 h	40	58:42
12	$Zn(OTf)_2$ (5)	EtOAc	rt	18 h	nr	–
13	$Zn(OTf)_2$ (5)	DMF	rt	18 h	nr	–
14	$Zn(OTf)_2$ (5)	toluene	rt	18 h	nr	–
15	$Zn(OTf)_2$ (5)	$CHCl_3$	rt	18 h	nr	–
16	$Zn(OTf)_2$ (5)	DCE	rt	18 h	72	47:53
17	$Zn(OTf)_2$ (5)	MeCN	rt	18 h	96	72:28
18	$Zn(OTf)_2$ (10)	MeCN	rt	5 min	95	72:28
19	$Zn(OTf)_2$ (20)	MeCN	rt	5 min	94	72:28
20	$Zn(OTf)_2$ (2)	MeCN	rt	5 min	93	72:28
21	$Zn(OTf)_2$ (2)	MeCN	0	18 h	nr	–
22	$Zn(OTf)_2$ (2)	MeCN	50	5 min	94	72:28

[a] Reaction conditions: *p*-quinone methide **1a** (0.3 mmol), benzoxazine **2a** (0.2 mmol), catalyst, solvent (3 mL).
[b] Determined by ^{1}H NMR analysis of crude product **3**.
[c] nr = no reaction.

Brønsted acids, temperature conditions, or $Zn(OTf)_2$ concentrations (entries 21 and 22). The reaction proceeded with complete regioselectivity, as confirmed by ^1H NMR analysis of the product. Notably, although the reaction was completely regioselective, the diastereoselectivity was only moderate to acceptable.

To support the generality of our methodology, we next explored the scope of the reaction with respect to the *p*-QMs **1a–g** and the benzoxazines **2a** and **2c** (Scheme 1). We were pleased to find that a broad range of *p*-QMs bearing electron-withdrawing or electron-donating substituents underwent reaction with benzoxazines to furnish the cor-

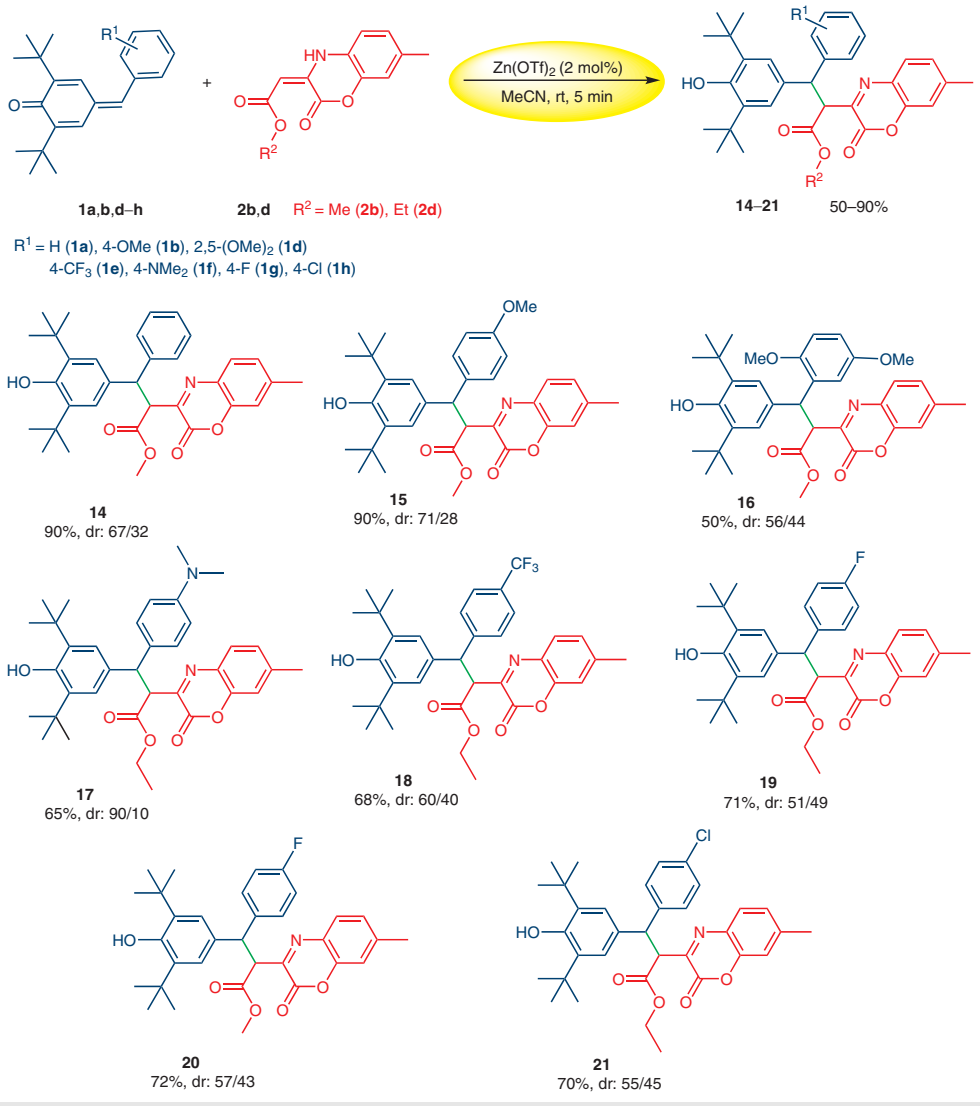


Scheme 1 Substrate scope of *p*-quinone methides **1a–h** with benzoxazinones **2a** and **2c**

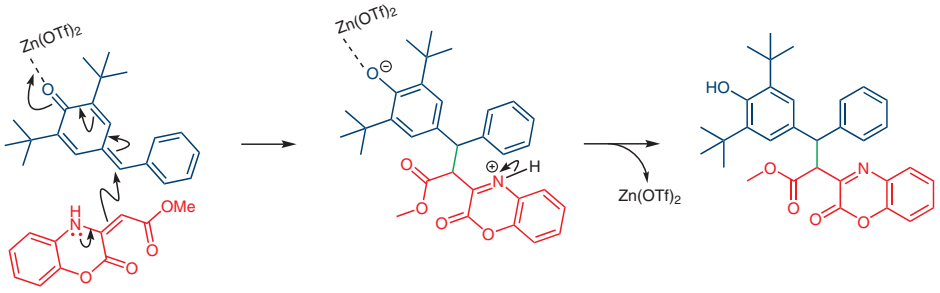
responding products **3–13** in yields of 54–95%. Much to our satisfaction, the electronic properties of the aryl substituents were shown to have little influence on the efficiency of the reaction. Both electron-releasing groups (R^1 = H, OMe, NMe_2) and electron-withdrawing groups (R^1 = F, Cl, CF_3), as well as dimethoxy substituents on the benzene ring, were well tolerated, giving the corresponding products **3–13** in good to excellent yields.

The reaction of **1a** with benzoxazinone **2a** under optimal condition gave the product **3** in 93% yield in five minutes (Scheme 1). Similarly, the reaction of *p*-QM **1b**, bearing a methoxy group in the *para*-position of benzene ring, with **2a** proceeded smoothly to give the corresponding product **4** in 95% yield in five minutes. The reaction of *p*-QM **1c** bearing two methoxy groups in the *meta*-positions of the benzene ring with **2a** was completed in 20 minutes and provided the **6** in 87% yield and with a good diastereoselectivity (dr 92:8). Furthermore, the reaction of *p*-QM **1d** with **2c** proceeded smoothly and reached completion within 10 minutes to furnish the corresponding product **7** without much diastereoselection. *p*-QMs **1e–h** bearing such groups as CF_3, NMe_2, fluoro, or chloro, on treatment with benzoxazinones **2a** and **2c**, gave the corresponding products **8–13** in good yields, but with diminished diastereoselectivity. Although the nature of the substituents on the benzene ring of the *p*-QM is influential in governing the diastereoselectivity of the product, no definitive pattern can be discerned.

Next, we turned our attention toward the scope and tolerance of the reaction of benzoxazinones with an electron-donating group on the arene moiety. Here, the reactions of benzoxazinones **2b** and **2d** with a 7-methyl substituent were completed in five minutes, and gave the correspond-



Scheme 2 Substrate scope of vinylogous carbamates **2b** and **2d** with *p*-QMs **1**



Scheme 3 Plausible reaction mechanism for the reaction between *p*-QMs **1** and benzoxazinones **2**

ing products **14–21** in good to high yields (Scheme 2). The diastereoselectivity of these reactions was comparable to that obtained from the reactions of benzoxazinones **2a** and **2c**. The reaction of *p*-QM **1a** with methyl (2*E*)-(5-bromo-2-oxo-2*H*-1,4-benzoxazin-3(4*H*)-ylidene)acetate provided only traces of the corresponding product, whereas the reaction of **1a** with the corresponding 5-nitro derivative did not proceed at all.

The assigned structures of the products were based on spectroscopic evidence, such as ^{1}H NMR (400 and 500 MHz), ^{13}C (100 MHz and 125 MHz), and HRMS data. Attempted to separate the diastereomers by methods such as crystallization and column chromatography were not successful. Nevertheless, we obtained crystals of diastereomers **7** and **16**, and their ORTEP diagrams[27] are shown Figure 1. This further confirmed the structures of the products.

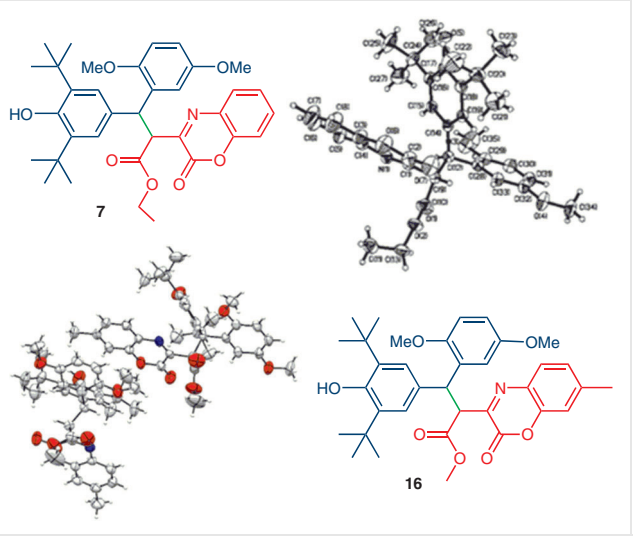


Figure 1 ORTEP diagrams of compounds **7** and **16**

Based on a previous report,[19] a plausible reaction mechanism for this transformation is shown in Scheme 3. The *p*-QM **1** is activated by the Lewis acid Zn(OTf)$_2$, leading to the generation of a highly electrophilic methylenic carbon at C-6. Subsequent attack of the nucleophilic carbon of benzoxazinone **2** on activated *p*-QM **1** and proton transfer result in the formation of the desired 1,6-conjugate addition product.

In summary, an efficient process for the synthesis of highly substituted functionalized *p*-QMs derivatives has been developed through an acid-catalyzed extended conjugation.[28] This reaction permits the formation of 3,3-diaryl-2-(2-oxo-2*H*-1,4-benzoxazin-3-yl)propanoic acid esters containing both phenolic and vinylogous carbamate units in good to excellent yields under mild conditions. The reaction displayed excellent regioselectivity. This novel, green, metal-free arylation strategy shows a good substrate scope and a broad functional-group tolerance.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1706600.

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(27) CCDCs 2015516 and 2012570 contain the supplementary crystallographic data for compounds **7** and **16**, respectively. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
(28) **3,3-Diaryl-2-(2-oxo-2*H*-1,4-benzoxazin-3-yl)propanoate Esters 3–21: General Procedure**

The appropriate benzoxazine **2** (0.5 mmol) was added to a stirred solution of the appropriate *p*-QM derivative **1** (0.6 mmol) in MeCN (3 mL), and the mixture was stirred at rt. $Zn(OTf)_2$ (2 mol%) was added, and the mixture was stirred at rt until the reaction was complete (TLC). The crude mixture analyzed by ^{1}H NMR to determine the dr of the diastereomers, then purified by chromatography on a short column [silica gel (100–200 mesh), EtOAc–hexanes (5:95)].

Methyl 3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-(2-oxo-2*H*-1,4-benzoxazin-3-yl)-3-phenylpropanoate (3)

Reaction time: 5 min. White solid; yield: 5 mg (93%); mp 146.4–147.6 °C (mixture of diastereomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.78 (d, *J* = 8.0 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 2 H), 7.43 (t, *J* = 8.0 Hz, 2 H), 7.34–7.28 (m, 4 H), 7.23–7.13 (m, 4 H), 7.04 (t, *J* = 8.0 Hz, 1 H), 6.96 (s, 2 H), 5.29 (d, *J* = 4.0 Hz, 1 H), 5.25 (d, *J* = 4.0 Hz, 1 H), 5.07–5.02 (m, 1 H), 4.93 (d, *J* = 12.0 Hz, 1 H), 4.91 (s, 1 H, O*H*), 3.56 (s, 3 H), 3.47 (s, 1 H), 1.41 (s, 7 H), 1.21 (s, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 170.0, 154.2, 152.4, 152.1, 146.1, 142.6, 135.8, 135.7, 131.3, 131.2, 131.1, 129.3, 128.6, 127.8, 125.5, 116.3, 52.6, 34.4, 34.2, 30.4, 30.1. HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{32}H_{35}NNaO_5$: 536.2407; found: 536.2408.