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A new chemical access for 3′-acetyl-4′-hydroxychalcones using borontrifluoride–etherate via a regioselective Claisen-Schmidt condensation and its application in the synthesis of chalcone hybrids

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ABSTRACT

A new chemical access has been developed for the synthesis of 3′-acetyl-4′-hydroxychalcones from 1-(5-acetyl-2-hydroxy-phenyl)-ethanone and various substituted benzaldehydes via a regioselective Claisen-Schmidt condensation using borontrifluoride–etherate ($BF_3{\cdot}OEt_2$) at room temperature, in good to excellent yields within 12–24 h. Application of this methodology has also been demonstrated in the synthesis of chalcone hybrids.

Chalcones are the main precursors for the biosynthesis of flavonoids, which are frequent components of the human diet. Licochalcone A (**I**) isolated from the roots of *Glycyrrhiza inflata* (licorice) has in vitro and in vivo antimalarial[1] and antileishmanial activities,[2] 3-methoxy-4-hydroxyloncocarpin (**II**) isolated from the roots of *Lonchocarpus utilis* inhibits the NADH:ubiquinone oxidoreductase activity[3] and synthetic chalcones such as 2,4-dimethoxy-4′-allyloxychalcone (**III**) and 2,4-dimethoxy-4′-butoxychalcone (**IV**) have been reported as antileishmanial agents[4] (Fig. 1). Recent studies of some of the chalcones on biological evaluation were found to be anticancer,[5] anti-inflammatory,[6] antimitotic,[7] antitubercular,[8] cardiovascular,[9] cell differentiation inducing,[10] nitric oxide regulation modulatory[11], and antihyperglycemic agents.[12]

Of the many methods available for the synthesis of chalcones, the most widely used method is the base catalyzed Claisen–Schmidt reaction in which the condensation of a ketone with an aldehyde is carried out in the presence of aq NaOH,[13] KOH,[14] $Ba(OH)_2$,[15] hydrotalcites,[16] LiHDMS[17], and calcined $NaNO_3$/natural phosphates.[18] The acid catalyzed methodologies include the use of $AlCl_3$,[19] dry HCl,[20] $Zn(bpy)(OAc)_2$,[21] $TiCl_4$,[22] $Cp_2ZrH_2/NiCl_2$,[23] Zeolites[16], and $RuCl_3$.[24]

Recently, we utilized $BF_3{\cdot}OEt_2$ as a condensing agent in the synthesis of chalcones,[25] stilbenes,[26] regioselective deacetylation of polyacetoxyacetophenones,[27] and synthesis of chromano-chalcones via regioselective cyclization of prenylated chalcones in high yields.[28] We also reported the antimalarial activity of naturally occurring prenylated chalcones,[29] and antileishmanial activity of natural chromenodihydrochalcones and synthetic chromenochalcones.[30] In continuation of our drug discovery program on antiparasitic agents, we wanted to synthesize chalcone hybrids, which contain chalcone core moiety with coumarin (**VI**), flavone (**VII**), benzofuran (**VIII**) skeleton and evaluate their advanced biological activities (Fig. 2).

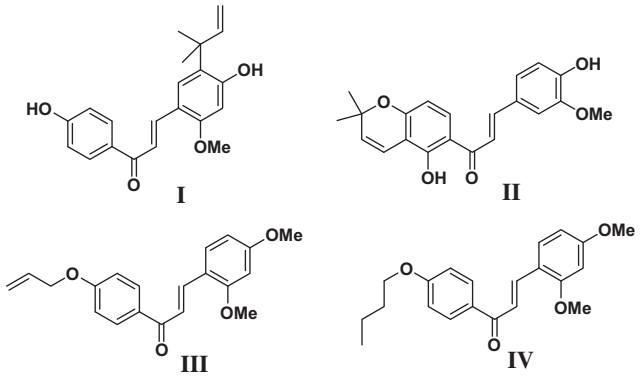

Figure 1. Natural and synthetic chalcones of biological importance.

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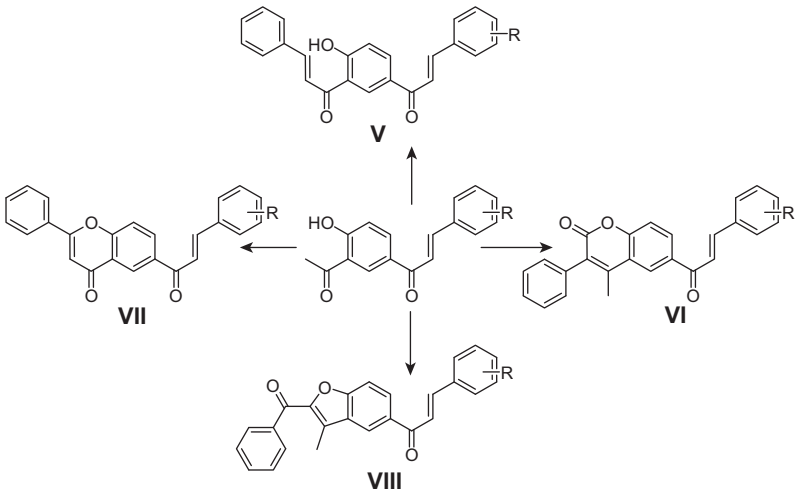
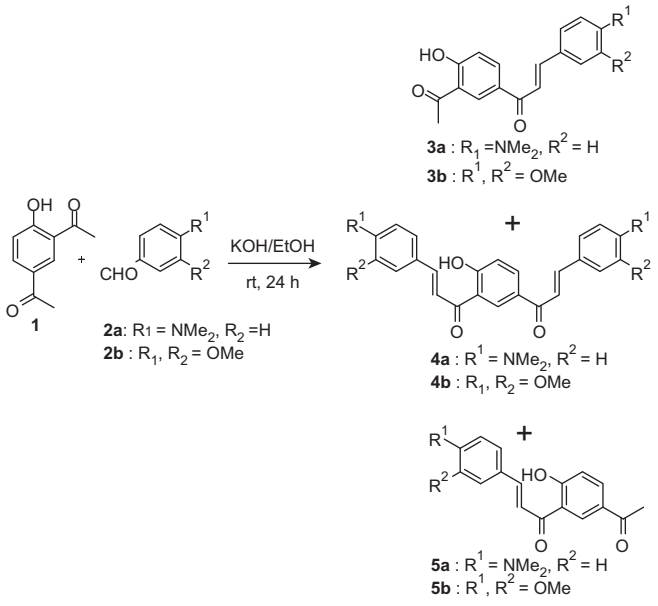
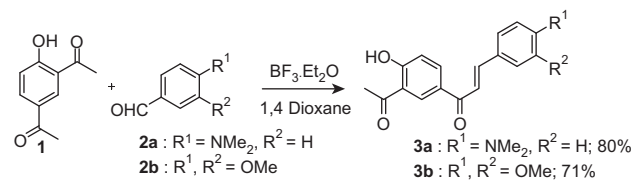


Figure 2. Examples for hybrid molecules with chalcone skeleton.



Scheme 1. Synthesis of chalcones via Claisen-Schmidt condensation using KOH in EtOH.



Scheme 2. Synthesis of acetylated chalcones via regioselective Claisen-Schmidt condensation reaction using $BF_3{\cdot}OEt_2$.

We therefore prepared the key starting material, 1-(5-acetyl-2-hydroxy-phenyl)-ethanone (**1**) by carrying out a Fries-rearrangement on *O*-acetylphenol[31] and planned to use one of the acetyl groups to generate the chalcone scaffold and utilize the second acetyl group to bring other functionalities such as bis-chalcone (**V**), coumarin (**VI**), flavone (**VII**), and benzofuran (**VIII**) (Fig. 2). Initially the diacetylated phenol **1** was subjected to Claisen-Schmidt condensation with 4-(dimethylamino)benzaldehyde (**2a**) using aqueous KOH in ethanol (Scheme 1), which resulted in the synthesis of mixture of chalcones, **3a**, **4a** and **5a**.[32]

In our previous studies on the synthesis of chalcones using $BF_3{\cdot}OEt_2$, we observed that the acetophenones, which have a chelated hydroxyl failed to provide the chalcones via Claisen-Schmidt condensation reaction.[25] The acetyl group which is in chelation with the hydroxyl group might be forming a complex with $BF_3{\cdot}OEt_2$ to prevent the condensation reaction (Fig. 3). We therefore planned to explore the above described property of $BF_3{\cdot}OEt_2$ to perform the regioselective Claisen-Schmidt condensation reaction on **1**. On the basis of this background a reaction was attempted using the same reactants (**1** and **2a**/**2b**) as described for KOH with $BF_3{\cdot}OEt_2$, which provided the desired acetylated chalcone **3a** and

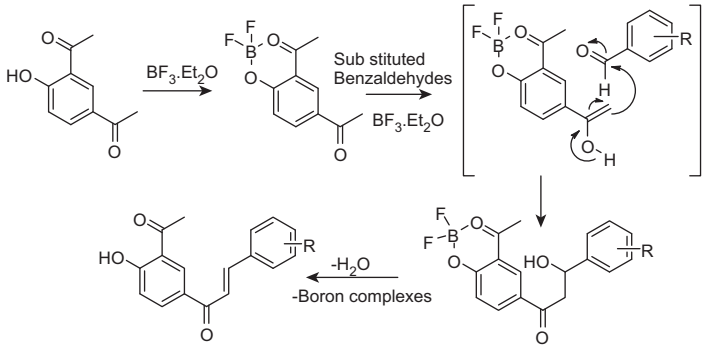


Figure 3. Possible reaction mechanism in the formation of acetylated chalcones using $BF_3{\cdot}OEt_2$.

Table 1
Regioselective synthesis of chalcones using $BF_3{\cdot}OEt_2$

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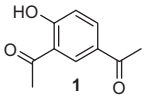
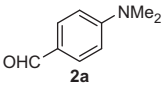
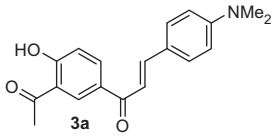
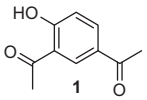
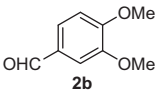
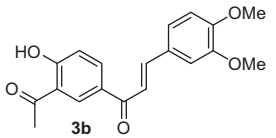
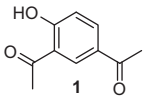
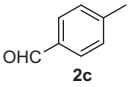
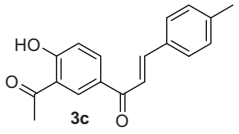
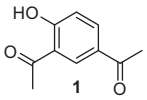
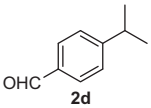
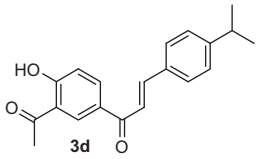
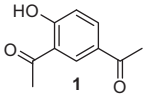
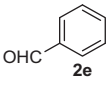
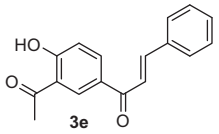
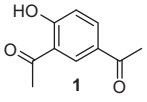
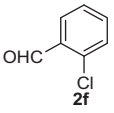
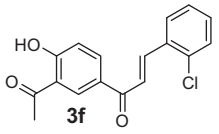
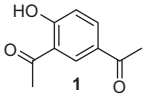
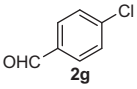
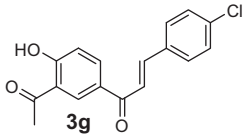
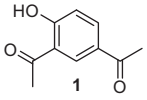
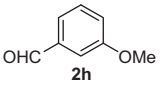
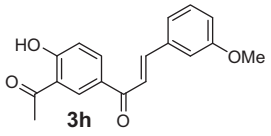
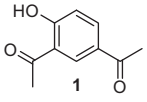
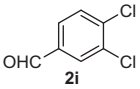
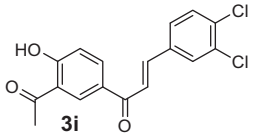
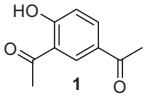
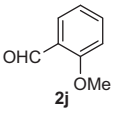
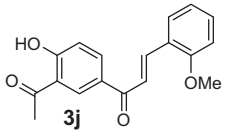
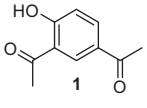
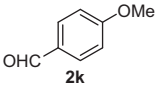
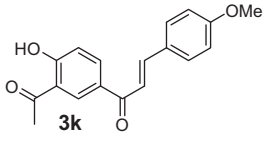
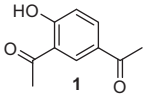
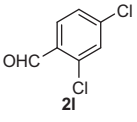
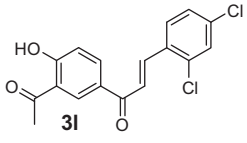
1				80
2				71
3				63
4				62
5				67
6				73
7				71
8				53
9				72
10				55
11				78
12				76

Table 1 (*continued*)

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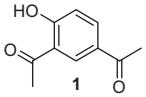
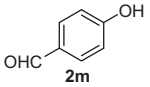
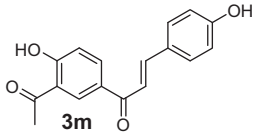
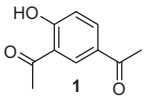
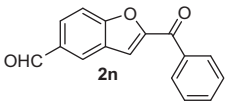
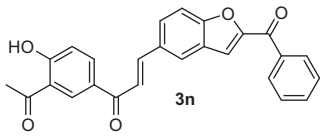
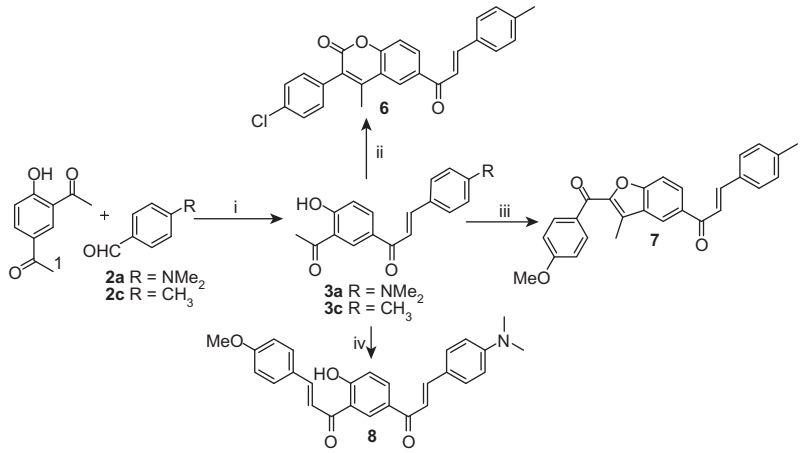
13				31
14				65

[a] Isolated yields.



Scheme 3. Synthesis of hybrid molecules (chalcone-coumarin, chalcone-benzofuran and bischalcone). Reagents and conditions: (i) $BF_3{\cdot}OEt_2$, 1,4-dioxane; (ii) *p*-Chlorophenylaceticacid, Ac_2O,TEA,16 h, heat; (iii) *p*-Methoxyphenacyl bromide, K_2CO_3, acetonitrile, 98 °C;(iv) 4-Methoxybenzaldehyde, KOH, EtOH, rt, 24 h.

3b respectively in good yields (Scheme 2).[33] Other Lewis acids such as $AlCl_3$, $ZnCl_2$, $SnCl_4$, and $TiCl_4$ failed to provide the products regioselectively.

To explore the generality of the reaction, we carried out a similar reaction with various substituted benzaldehydes **2c**–**2n**, which provided the desired acetylated chalcones **3c**–**3n** in good to excellent yields with the exception of **3m** (Scheme 2, Table 1). Starting materials were recovered in low yield reactions during column chromatography and we did not observe the formation of their regioisomers.

As described in our previous reports,[27,28] the reaction mechanism in the regioselective condensation reaction appears to be $BF_3{\cdot}OEt_2$'s complex formation with chelated hydroxyl and acetyl groups and second mole of $BF_3{\cdot}OEt_2$ might be participating in the condensation reaction with second free acetyl group to provide the desired acetylated chalcones (Fig. 3). Further studies are required to confirm the exact reaction mechanism.

To demonstrate the wide application of this methodology, the acetylated chalcone, **3c** was reacted with *p*-chlorophenylacetic acid in the presence of Ac_2O and triethylamine (TEA), which gave the coumarin-chalcone hybrid **6**.[34] Similarly **3c** upon reaction with *p*-methoxyphenacyl bromide provided us the bezofuran-chalcone hybrid **7**.[35] Claisen-Schmidt condensation of **3a** with *p*-methoxybenzaldehyde using KOH resulted in the synthesis of bischalcone **8** (Scheme 3).[32]

In conclusion, a new chemical access has been developed for the synthesis of 3′-acetyl-4′-hydroxychalcones via a regioselective Claisen-Schmidt condensation using $BF_3{\cdot}OEt_2$ for the first time. Other Lewis acids such as $AlCl_3$, $ZnCl_2$, $SnCl_4$, and $TiCl_4$ failed to provide the regioselective product. We also utilized these intermediates to synthesize the hybrid molecules such as bischalcones, coumarin-chalcone, and benzofuran-chalcone to evaluate their biological potential. This standardized method can be used to generate a large number of hybrid molecules of biological importance.

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Supplementary data

Supplementary data (compounds characterization data and spectra (NMR and Mass) of all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.08.120.

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32. *Representative procedure for the synthesis of, chalcones **3a**, **5a** and bischalcone **4a**.* To a solution of 1-(5-acetyl-2-hydroxy-phenyl)-ethanone (**1**) (200 mg, 1.12 mmol) in aqueous potassium hydroxide (2 pellets) in ethanol (5 mL) was added the 4-(dimethylamino)benzaldehyde (**2a**) (167 mg, 1.12 mmol). The whole reaction mixture was kept at room temperature for 24 h. After it was quenched in ice-cold water, and acidified with 1 N HCl. The crude product was extracted with ethyl acetate (3 x 50 mL), washed with brine solution and the combined organic layer was concentrated under reduced pressure. The crude product was subjected to silica gel column chromatography using mixture of hexane-ethyl acetate (95:5 to 90:10) as a mobile phase to afford chalcones **3a** (150 mg, 43%), **5a** (50 mg, 14%), and bischalcone **4a** (80 mg, 16%).
Compound **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.89 (s, 1H), 8.65 (d, J = 2.1 Hz, 1H), 8.08 (dd, J = 1.4 Hz, 8.7 Hz, 1H), 7.97 (d, J = 15.0 Hz, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.56 (d, J = 15.0 Hz, 1H), 7.07 (d, J = 8.7 Hz, H), 6.75 (d, J = 7.8 Hz, 2H), 3.10 (s, 6H), 2.40 (s, 3H); MS (ESI) m/z 310 $(M+H)^+$.
Compound **4a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.79 (s, 1H), 8.71 (d, J = 2.7 Hz, 1H), 8.16 (dd, J = J = 1.0 Hz, 8.7 Hz, 1H), 7.94 (d, J = 16.7 Hz, 1H), 7.88 (d, J = 15.1 Hz, 2H), 7.64 (m, 5H), 7.55 (d, J = 15.1 Hz, 1H), 7.09 (d, J = 13 Hz, 2H), 6.73 (d, J = 13 Hz, 4H), 3.08 (s, 6H), 3.05 (s, 6H); MS (ESI) m/z 441 $(M+H)^+$.
Compound **5a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 12.66 (s, 1H), 8.53 (d, J = 2.7 Hz, 1H), 8.20 (dd, J = 2.0 Hz, 8.8 Hz, 1H); 7.87 (d, J = 15.3 Hz, 1H), 7.60 (m, 2H), 7.35 (d, J = 15.3 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H), 6.74 (d, J = 8.8 Hz, 2H), 3.07 (s, 6H), 2.76 (s, 3H); MS (ESI) m/z 310 $(M+H)^+$.
33. *Representative procedure for the synthesis of acylatedchalcone **3a**.* To a stirred solution of **1** (100 mg, 0.56 mmol) and 4-(dimethylamino)benzaldehyde (**2a**) (83 mg, 0.56 mmol) in dry 1,4 dioxane was added gradually $BF_3{\cdot}OEt_2$ (0.142 mL, 1.12 mmol) at room temperature. The whole reaction mixture was stirred for 24 h. The reaction mixture was then diluted with ethyl acetate (100 mL) and washed with water (3 x 25 mL) to decompose the $BF_3{\cdot}OEt_2$ complex. The organic solution obtained after extraction was dried over anhyd. Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude product was purified by silica gel column chromatography using hexane-ethyl acetate (93:7) as a mobile phase to afford **3a**. (140 mg, 80%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 13.89 (s, 1H), 8.65 (d, J = 2.1 Hz, 1H), 8.08 (dd, J = 1.4 Hz, 8.7 Hz, 1H), 7.97 (d, J = 15.0 Hz, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.56 (d, J = 15.0 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H), 6.75 (d, J = 7.8 Hz, 2H), 3.10 (s, 6H), 2.40 (s, 3H); MS (ESI) m/z 310 $(M+H)^+$.
34. *General procedure for the synthesis of coumarin-chalcone hybrid **6**.* A mixture of acetylated chalcone **3c** (100 mg, 0.35 mmol), *p*-chlorophenylacetic acid (182 mg, 0.35 mmol), acetic anhydride (3 mL), and TEA (1.2 mL) was refluxed for 16 h, then cooled to room temperature and poured on to ice-water. The separated solid was filtered, washed successively with aq. sodium bicarbonate, water and crystallized from methanol to obtain the desired compound **6** (95 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 15.6 Hz, 1H), 7.60 (d, J = 15.6 Hz, 1H), 7.56 (m, 2H), 7.47 (m, 3H), 7.25 (m, 4H), 2.43 (s, 6H);); ^{13}C (50Mz, $CDCl_3$) δ 188.3, 160.3, 155.5, 148.2, 146.2, 141.9, 134.8, 132.6, 132.1, 131.7 (4C), 130.9 (2C), 129.1 (3C), 128.9 (2C), 126.5, 120.8, 120.4, 117.3, 21.8, 17.0; MS (ESI) m/z 415 $(M+H)^+$.
35. *General procedure for the synthesis of benzofuran-chalcone hybrid **7**.* A mixture of *p*-methoxyphenacyl bromide (81 mg, 0.35 mmol), acetylated chalcone **3c** (100 mg, 0.35 mmol) and K_2CO_3 (49 mg, 0.35 mmol) was taken up in 5 mL of acetonitrile (CH_3CN) and stirred continuously. The heterogeneous mixture was heated at reflux for 3 h under atmosphere of N_2 until the transformation was complete (TLC). After the heat source was removed, 20 mL of water was added, and the reaction mixture was allowed to cool to ambient temperature. The mixture was filtered, washed with H_2O/CH_3CN; 2:1, CH_3CN and then dried to give desired compound **7** in (105 mg, 72%), ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 8.23 (m, 3H), 7.90 (d, J = 15.6 Hz, 1H), 7.64 (d, J = 15.6 Hz, 1H), 7.62 (m, 3H), 7.25 (d, J = 6.9 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H), 3.93 (s, 3H), 2.74 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.4, 184.3, 163.8, 156.6, 150.1, 145.4, 141.5, 134.5, 132.6 (2C), 132.4, 130.5, 129.7 (2C), 128.8, 128.7 (2C), 128.4, 126.7, 123.0 121.2, 114.0 (2C), 112.6, 55.8, 21.8, 10.3; MS (ESI) m/z 411 $(M+H)^+$.