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Synthetic study of kosinostatin aglycone: synthesis of BCDE rings using alkoxycarbonylmethylation of diazonaphthoquinone

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ABSTRACT

A synthetic study of kosinostatin aglycone is reported. Synthesis of key intermediate lactone **3**, which corresponds to the BCDE ring fragment, was accomplished, and the precursor BCD ring fragment **5** was synthesized via two routes. First, **5** was synthesized from 2,5-dimethoxybenzaldehyde **16** by the combination of typical known transformations including efficient application of non-aqueous OsO_4 oxidation in the presence of $PhB(OH)_2$. However the synthesis required 15 long steps, and its main difficulty was *ortho*-alkoxycarbonylmethylation of 1-naphthol. Next we attempted to apply our recently developed alkoxycarbonylmethylation of diazonaphthoquinone for the synthesis of **5**, and **5** was successfully synthesized in 9 steps from the same starting compound **16**. Finally, **5** was stereoselectively converted to lactone **3** via trifluoroacetic acid-mediated cyclization of the 3,4-epoxycylohexanecarboxylic acid derivative.

The quinocycline/isoquinocyline antibiotics[1,2] constitute a class of natural products, and show several antibiotic and cytotoxic activities (Fig. 1). In the 1950s, quinocyclines were first isolated from *Streptomyces aureofaciens*[1] and the structure of isoquinocycline A was confirmed by X-ray analysis in 1968.[1e] Although the structure of quinocycline A and B was unclear, quinocycline B was also isolated from *Micromonospora* sp. TP-A0468 (along with isoquinocycline B)[2a,2b] as kosinostatin in 2002, and the structure was fully assigned by NMR experiments. Recently, kosinostatin was also isolated from *Streptomyces violaceusniger* Strain HAL64. [2c]

Quinocyclines/isoquinocyclines have a unique structure consisting of a tetrahydronaphthacenequinone core (ABCD rings) having 3-chiral centers (C7, C9, C10) connecting the unusual pyrrolopyrrole (FG rings) via *N,O*-acetal, and a sugar. Stimulated by the unique structure, we have been studying the synthesis of kosinostatin aglycone **1**. Scheme 1 outlines our retrosynthesis plan. Aglycone **1** is simplified to tetracyclic lactone **3** by assuming the Diels–Alder reaction with diene **2**[3] and nucleophilic addition of vinylamidine moiety **4**. Three carbon chiral centers in D rings of lactone **3** were assumed to be constructed by the oxidative cyclization of alkenyl carboxylic acid;[4] therefore, ester **5** was set as its precursor. The D ring in **5** was expected to be constructed by olefin metathesis of diene **6**,[5] which, in turn, could be derived from 1-naphthalenol **8** by the *ortho*-alkoxycarbonylmethylation and the successive introduction of a methallyl group at the activated methylene position in **7**.

Recently, Koert and co-workers reported the synthesis of CDEFG rings **15** of isoquinocyclines (Scheme 2).[6] First, lactone **12** was synthesized via iodo lactonization of carboxylic acid **11** and then introduction of **13** or **14** as a unit of A ring to lactone **12**, which was transformed to **15** by several steps. For the synthesis of quinocyclines' aglycone based on Koert's strategy, preparation of an *ortho*-alkoxycarbonylmethyl 1-naphthol derivative [α-(1-hydroxyl-2-naphthyl)ester] such as **7** or 2-alkoxycarbonylmethyl 1-anthranol derivative [α-(1-hydroxy-2-anthryl)ester] may be

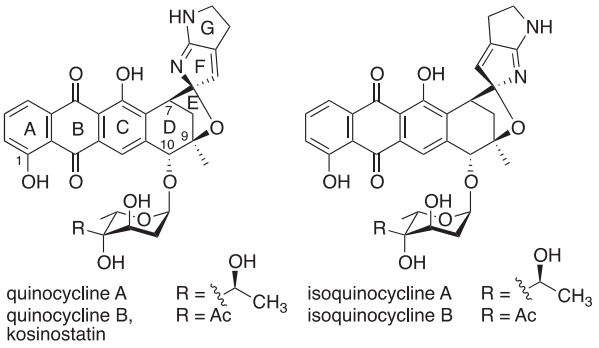

Figure 1. Quinocycline/isoquinocycline antibiotics.

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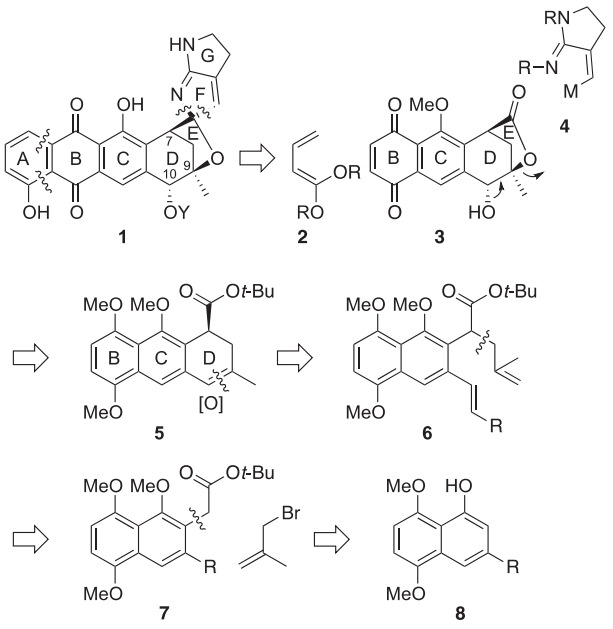
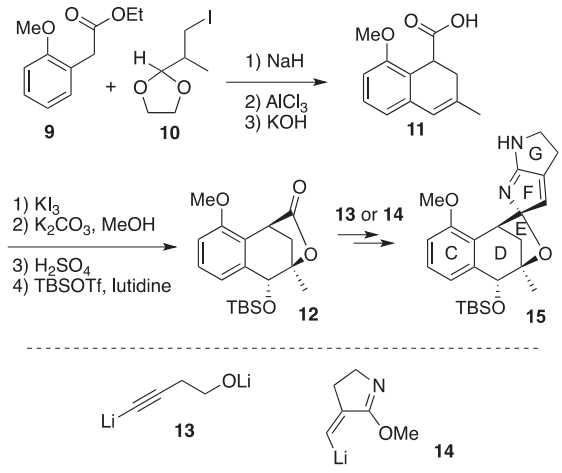


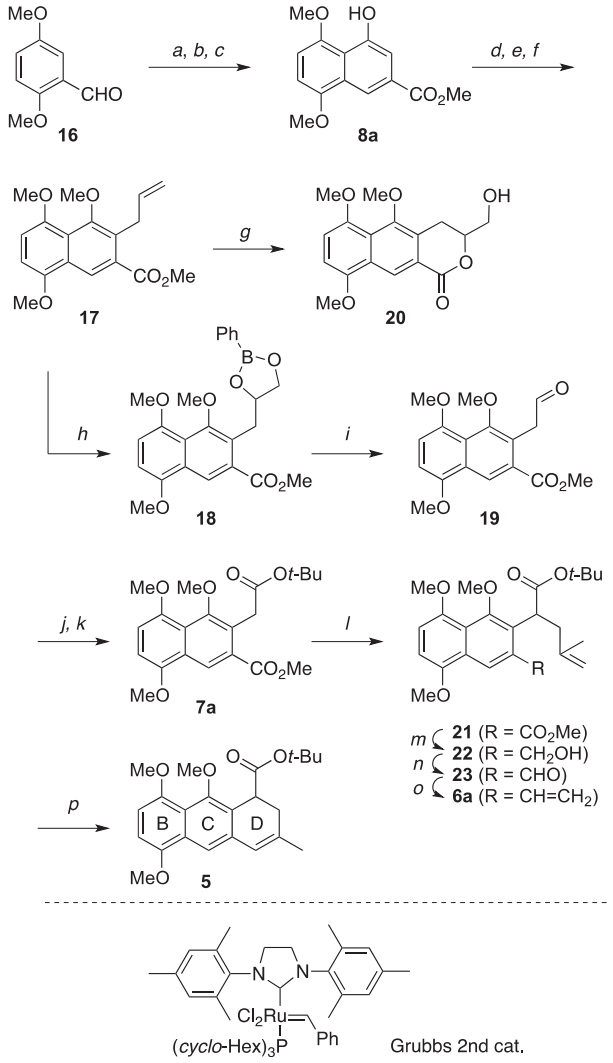
Scheme 1. Retrosynthesis of kosinostatin aglycone **1**.



Scheme 2. Koert's synthesis of CDEFG rings of isoquinocyclins.

needed. In our synthetic plan, *ortho*-alkoxycarbonylmethylation of 1-naphthol is required. However, there are few efficient methods for the synthesis of α-(*ortho*-hydroxyaryl)esters from phenol derivatives. In this study, we describe the synthesis of the key intermediate lactone **3** for the synthesis of kosinostatin aglycone via two routes, including study of the *ortho*-alkoxycarbonylmethylation reaction to 1-naphthols.

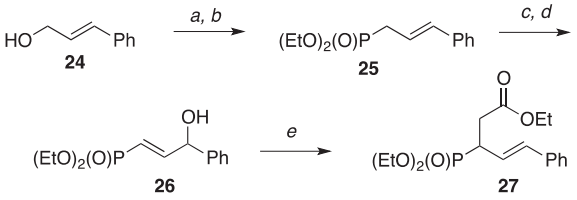
Synthesis of the BCD ring fragment **5** started with the readily available known 1-naphthol **8a**, which was synthesized from 2,5-dimethoxybenzaldehyde (**16**) in 3 steps via the Stobbe reaction with dimethyl succinate (Scheme 3).[7] For the introduction of an alkoxycarbonylmethyl group at the *ortho* position in 1-naphthol **8a**, the allyl group was selected as its equivalent.[8] After O-allylation of naphthol **8a**, Claisen rearrangement followed by O-methylation of the thus-formed naphthol gave 2-allyl naphthalene **17**. Although ozonolysis of alkene **17** was unsuccessful, **17** was efficiently transformed to aldehyde **19** via non-aqueous OsO_4 oxidation in the presence of $PhB(OH)_2$ and the successive $NaIO_4$ oxidation following Narasaka's procedure.[9–11] When **17** was subjected to general aqueous OsO_4 reaction conditions, lactone **20** was obtained



Scheme 3. Synthesis of BCD ring fragment **5** (1st generation). Reagents and conditions: (a) Dimethyl succinate, NaH, cat. MeOH, toluene, rt, 3 h; (b) NaOAc, Ac_2O, 140 °C, 3 h (2 steps 58%); (c) K_2CO_3, MeOH, rt, 3 h (63%); (d) $CH_2{=}CHCH_2Br$, K_2CO_3, acetone, 60 °C, 5 h (74%); (e) DMF, 180 °C, 4 h (67%); (f) MeI, K_2CO_3, DMF, 80 °C, 6 h (66%); (g) 5 mol % microencapsulated OsO_4,[11] NMO, H_2O, acetone, CH_3CN, rt, 4 days (51%); (h) 7 mol % OsO_4, NMO, $PhB(OH)_2$, Na_2SO_4, CH_2Cl_2, rt, 20 min; (i) $NaIO_4$, THF, H_2O, 50 °C, 1.5 h (2 steps 83%); (j) $NaClO_2$, $Me_2C{=}C(H)Me$, NaH_2PO_4, *t*-BuOH, H_2O, rt, 1 h; (k) Boc_2O, DMAP, *t*-BuOH, rt, 5 h (2 steps 62%); (l) NaH, $CH_2{=}C(CH_3)CH_2Br$, DMF, rt, 5.5 h (71%); (m) $LiAlH_4$ (3 equiv), THF, −78 → −30 °C, 1.5 h (92%); (n) SO_3·pyridine, Et_3N, DMSO, rt, 8 h (90%); (o) $Ph_3P^+CH_3{\cdot}Br^-$, *t*-BuOK, THF, rt, 30 min (98%); (p) Grubbs 2nd cat., toluene, 80 °C, 6 h (96%).

mainly. After the transformation of aldehyde **19** to *tert*-butyl ester **7a**, a methallyl group was introduced at the active methylene part to afford diester **21**. Selective reduction of the methyl ester in **21** was appropriately achieved with $LiAlH_4$ at −30 °C without touching the *tert*-butyl ester to give alcohol **22**. Oxidation of the alcohol followed by the Wittig reaction gave diene **6a**, whose intramolecular olefin metathesis using Grubbs catalyst (2nd generation)[5] smoothly proceeded to afford BCD ring fragment **5**.

Although the BCD ring fragment **5** was synthesized from commercially available aldehyde **16**, it required 15 long steps. The following two are the difficult transformations in Scheme 3: (i) introduction of the alkoxycarbonylmethyl group to 1-naphthol **8a**, and (ii) transformation of the methyl ester in **8a** to an alkenyl moiety, whose ester's origin is dimethyl succinate on the Stobbe reaction. The former process was expected to be improved by alkoxycarbonylmethylation using diazonaphthoquinone, which



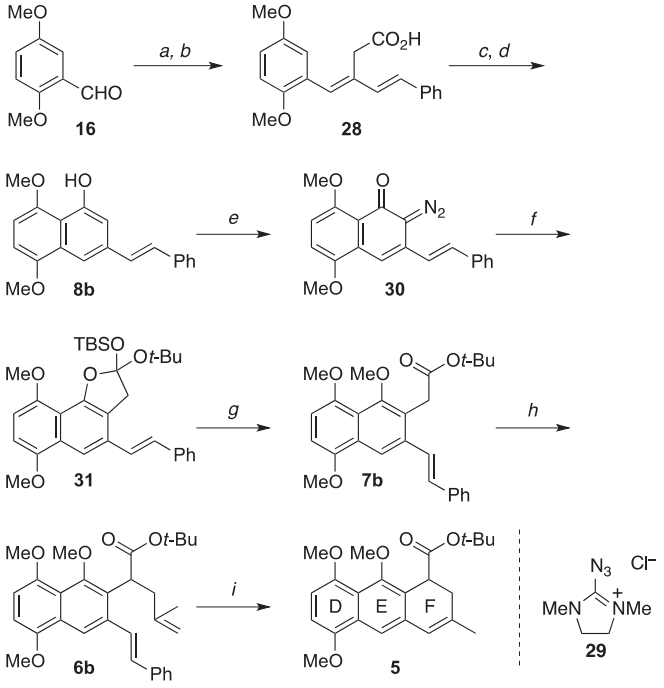
Scheme 4. Synthesis of phosphonate **27**. Reagents and conditions: (a) $SOCl_2$ (1.05 equiv); (b) $P(OEt)_3$ (1 equiv), 150 °C, 12 h; (c) *m*-CPBA (1.7 equiv), $NaHCO_3$ (0.2 equiv), CH_2Cl_2, rt, 72 h (97%); (d) NaOMe, MeOH, 0 °C, 6.5 h (76%); (e) $CH_3C(OEt)_3$ (5 equiv), $CH_3CH_2CO_2H$, 150 °C, 8 h (65%).

was recently developed in our laboratory.[12] For the latter problem, we planned to study the Horner–Wittig reaction of aldehyde **16** with phosphonate **27** that is ready arranged alkenyl moiety for olefin metathesis. Then, we tried the synthesis of BCD rings **5** by the new route.

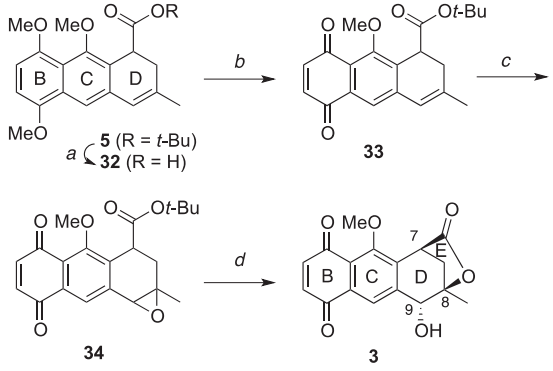
Phosphonate **27** was synthesized from alcohol **24** by reference to the synthesis of similar phosphonates (Scheme 4).[13] Transformation of alcohol **24** to the corresponding chloride followed by the Arbuzov reaction gave allyl phosphonate **25**.[14] *m*-Chloroperoxybenzoic acid (*m*-CPBA) oxidation of **25** gave the corresponding epoxide, which was treated with sodium methoxide, giving allylic alcohol **26**. The Johnson–Claisen rearrangement of **26** with $CH_3C(OEt)_3$ proceeded to afford phosphonate **27** having a styryl group.[15]

The Wittig–Horner reaction of aldehyde **16** with phosphonate **27** gave the corresponding unsaturated ester, whose ester was hydrolyzed to give unsaturated acid **28** (Scheme 5). Treatment of **28** with acetic anhydride in the presence of sodium acetate gave naphthyl acetate, which was hydrolyzed to give naphthol **8b**. Diazo-transfer reaction for **8b** by 2-azido-1,3-dimethylimidazolinium chloride (ADMC, **29**) formed by the reaction of 2-chloro-1,3-dimethylimidazolinium chloride (DMC) and sodium azide smoothly proceeded to afford corresponding diazonaphthoquinone **30**.[16] Rhodium-catalyzed cyclization of **30** with ketene silyl acetal followed by a ring opening reaction successfully proceeded to afford alkoxycarbonylmethylated naphthalene **7b** in 36% yield in 3 steps from 1-naphthol **8b**.[12] Introduction of a methallyl group to the active methylene part in **7b** proceeded to afford diene **6b**, whose intramolecular olefin metathesis proceeded to afford the DEF ring fragment **5**. By the new synthetic route for **5**, the number of reaction steps was reduced by 6, from 15 to 9 steps, and the total yield was increased to 8.6% yield from 3.4% yield compared to the former synthetic route (Scheme 3).

Next we tried the transformation of **5** to lactone **3** (Scheme 6). Several reports have appeared about the oxidative cyclization of cyclohex-3-encarbonic acid to the corresponding hydroxy lactone via epoxide.[4] However, epoxidation of the alkene in the D ring of ester **5** or the corresponding carboxylic acid **32** was unsuccessful because of over oxidation of aromatic rings. Selective oxidation of the electron-rich B ring in **5** was performed by ceric ammonium nitrate (CAN) to give quinone **33**, whose D ring's epoxidation was accomplished by the treatment of *m*-CPBA to afford **34** as a ca 1/1 diastereomer mixture. The products were rather unstable, and the crude material was treated with trifluoroacetic acid to obtain lactone **3**.[17] The structure/stereochemistry of **3** was identified by NMR experiments (^{1}H NMR, NOE), as shown in Figure 2. That is, the ^{1}H NMR signal of H_a of the hydroxyl group was observed as a doublet (J = 7.5 Hz) at 6.50 ppm in DMSO-d_6, which was eliminated by the addition of D_2O, and NOE was detected between H_a and H_b (2.14 ppm). These data suggested that the product from **34** was not δ-lactone but γ-lactone, and oxygen functional groups attached at C8 and C9 in the D ring are placed in the *anti* position, as shown for compound **3**.



Scheme 5. Synthesis of BCD ring fragment **5** (2nd generation). Reagents and conditions: (a) **27** (1,2 equiv), NaH (3 equiv), THF, −78 °C to rt, 3.5 h (75%); (b) 10 M KOH aq *n*-Bu_4NBr (0.1 equiv), 1,4-dioxane, 90 °C, 24 h; (c) NaOAc (2 equiv), Ac_2O, 140 °C, 7 h; (d) K_2CO_3, MeOH, 1,4-dioxane, rt, 4.5 h (3 steps 42%); (e) DMC (5 equiv), NaN_3 (5 equiv), CH_3CN, −25 °C, 1.5 h: then **8b**, Et_3N (2.5 equiv), THF, −25 °C to rt, 3 h (89%); (f) CH_2=C(OTBS)(O*t*-Bu) (2 equiv), 1 mol % $Rh_2(OAc)_4$, 40 °C, 1 h (45%); (g) *n*-Bu_4NF (2 equiv), MeI (10 equiv), $Na_2S_2O_4$ (0.1 equiv), THF, rt, 1.5 h (91%); (h) CH_2=C(CH_3)CH_2Br, NaH, 45 °C, 3 h (91%); (i) 5 mol % Grubbs 2nd cat., toluene, 80 °C, 12 h (82%).



Scheme 6. Synthesis of BCDE ring fragment **3**. Reagents and conditions: (a) CF_3CO_2H, CH_2Cl_2, rt, 1.5 h (quant.); (b) $Ce(NH_4)_2(NO_3)_6$, CH_3CN, H_2O, 0 °C, 10 min; (c) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, rt, 2.5 h; (d) CF_3CO_2H, CH_2Cl_2, 0 °C, 40 min (3 steps 31%).

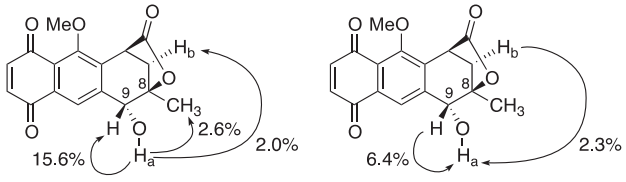


Figure 2. NOE experiment of lactone **3**.

In conclusion, toward the synthesis of kosinostatin aglycone **1**, we synthesized the key intermediate lactone **3**, which corresponds to the BCDE ring fragment. The precursor BCD ring fragment **5** was synthesized via two routes, and the improved 2nd generation synthesis includes efficient application of our developed alkoxycarbonylmethylation of diazonaphthoquinone. Currently, we are studying the construction of A and FG rings, aiming at the total synthesis of aglycone **1**.

Acknowledgments

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10. Although oxidative transformation of alkene **17** to aldehyde **19** proceeded by using microencapsulated OsO_4 (MC OsO_4),[11] the yield was lower (62% yield in 2 steps) than that of the reaction with OsO_4 [(i) cat. MC OsO_4, NMO, $PhB(OH)_2$, Na_2SO_4, acetone, rt, 13 h; (ii) $NaIO_4$, THF, H_2O, 50 °C, 1 h].
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15. *Spectral data of* ***27*****:** ^{1}H NMR (400 MHz, $CDCl_3$) 7.36 (d, 2H, J = 7.4 Hz), 7.29 (dd, 2H, J = 7.4, 7.3 Hz), 7.22 (t, 1H, J = 7.3 Hz), 6.58 (dd, 1H, J = 15.8, 4.9 Hz), 6.11 (ddd, 1H, J = 15.9, 9.0, 6.5 Hz), 4.11–4.01 (m, 6H), 3.30–3.18 (m, 1H), 2.85 (ddd, 1H, J = 4.1, 10.7, 15.8 Hz), 2.61 (ddd, 1H, J = 9.6, 10.3, 15.8 Hz), 1.27 (t, 3H, J = 7.1 Hz), 1.24 (t, 3H, J = 7.1 Hz), 1.16 (t, 3H, J = 7.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) 170.7 (d, J = 19.2 Hz), 136.4 (d, J = 3.1 Hz), 134.1 (d, J = 13.5 Hz), 128.3, 127.5, 126.2, 122.8 (d, J = 10.2 Hz), 62.4 (d, J = 6.9 Hz), 62.1 (d, J = 7.0 Hz), 60.6, 38.2 (d, J = 142.1 Hz), 34.0 (d, J = 3.0 Hz), 16.2 (d, J = 5.2 Hz), 14.0 ppm; IR (KBr) 3464, 2983, 1733, 1647, 1600, 1577, 1496, 1477, 1448, 1392, 1371, 1228, 1161, 1097, 981 cm^{-1}; HRMS (FAB$^+$) m/z [M+H]$^+$ calcd for $C_{17}H_{26}O_5P$ 341.3518. Found 341.1518.
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17. *Spectral data of* ***3*****:** ^{1}H NMR (500 MHz, DMSO-d_6) 7.95 (s, 1H), 7.02 (d, 1H, J = 10.2 Hz), 6.97 (d, 1H, J = 10.2 Hz), 6.50 (d, 1H, J = 7.5 Hz), 4.46 (d, 1H, J = 7.5 Hz), 4.17 (d, 1H, J = 4.7 Hz), 3.85 (s, 3H), 2.41 (dd, 1H, J = 12.0, 4.9 Hz), 2.14 (d, 1H, J = 12.0 Hz), 1.58 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) 184.2, 183.6, 174.8, 156.1, 143.7, 140.6, 137.4, 136.8, 133.4, 124.8, 123.3, 85.6, 70.9, 63.4, 39.4, 34.9, 21.8 ppm; IR (KBr) 3448, 2923, 2851, 1779, 1664, 1570, 1459, 1338, 1296, 1228, 1106, 1038, 930 cm^{-1}; HRMS (EI$^+$) m/z [M]$^+$ calcd for $C_{17}H_{14}O_6$ 314.0790. Found 314.0801.