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Synthesis of carbohydrate fused chiral macrocyclic benzolactones through Sonogashira reaction†

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Synthesis of 10-, 11- and 12-membered chiral benzolactones fused to furanose/pyranose sugars has been achieved in good to excellent yields using an intramolecular Sonogashira reaction. Positions 1–2, 3–5, 3–6 and 5–6 of sugar were utilized for the construction of the macrocycles. The requisite furanose/pyranose scaffolds were synthesized utilising conventional protection–deprotection strategies like benzylation, tritylation, detritylation, EDC coupling, propargylation, *etc.*

Macrolactones are widespread in nature and possess promising pharmacological properties such as enzyme inhibitory activity.[1] Macrocyclic benzolactones, in particular, are an ever-growing class of natural products with potential therapeutic and agrochemical applications.[2] For example, each of the macrocyclic benzolactones shown in Fig. 1 exhibit characteristic and unique type of biological activities.[3–6] Thus, the benzolactone core is clearly a biologically significant structural motif.

The synthesis of the macrocyclic framework is one of the important processes for producing natural and synthetic compounds useful in organic chemistry.[7] Two types of methodologies are mainly employed for the synthesis of macrolactones: (1) lactonization strategies (cyclization precursor must contain alcoholic and carboxyl groups as shown in Fig. 2) and (2) non-lactonization strategies (cyclization precursor need not contain alcoholic and carboxyl groups as shown in Fig. 3). The lactonization strategies include: (i) the Corey–Nicolaou *S*-pyridyl ester lactonization method,[8] (ii) the Masamune thiol ester activation method,[9] (iii) the Mukaiyama onium salt method,[10] (iv) the Yamaguchi mixed-anhydride method,[11] (v) the Keck–Steglich DCC/DMAP/HCl activation method,[12] (vi) the Mitsunobu alcohol activation method,[13] and (vii) the Shiina benzoic anhydride method,[14] while the non-lactonization strategies include: (i) ring closing metathesis (RCM),[15,16] (ii) multi-component Ugi reaction,[17] (iii)

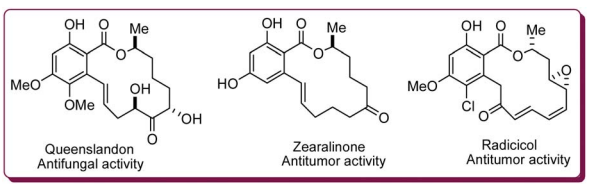

Fig. 1 Biologically significant naturally occurring macrocyclic benzolactones.

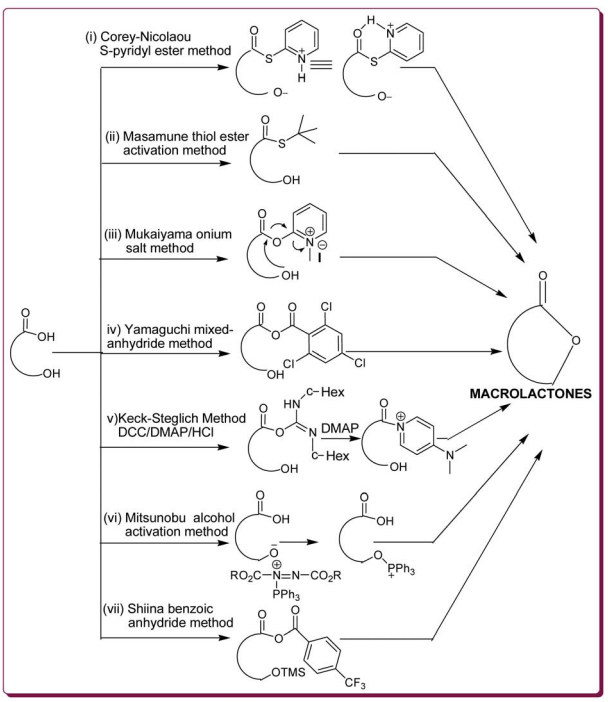

Fig. 2 Lactonization strategies for the synthesis of macrolactones.

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† Electronic supplementary information (ESI) available. See DOI: 10.1039/c3ra43827a

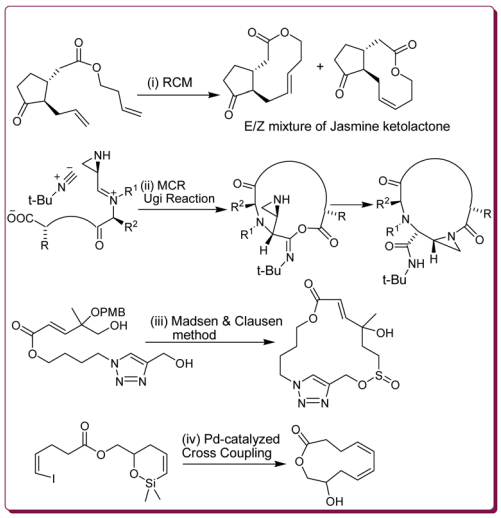
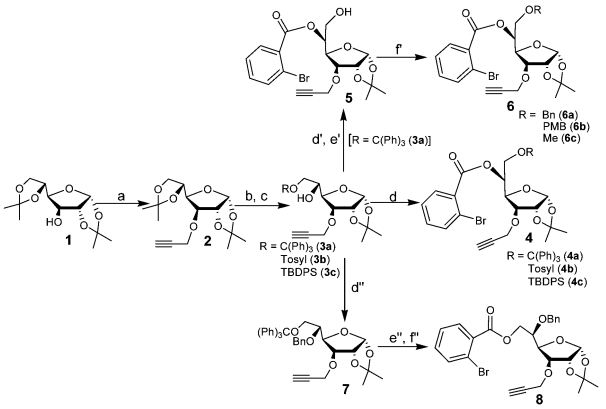


Fig. 3 Non-lactonization strategies for the synthesis of macrolactones.



Scheme 1 Scaffolds for Sonogashira reaction utilizing 3–5 and 3–6 positions of sugar. *Reagents and conditions*: (a) propargyl bromide, DCM : aq. NaOH, TBAB, 3 h, rt, 80%; (b) 70% AcOH in H_2O, 8 h, rt, 78%; (c) R–Cl, Py, 12 h [R = trityl (**3a**, 65%) or tosyl (**3b**, 81%)] or TBDPSCl (for compound **3c**), imidazole, dry DMF, N_2 atm, rt, 85%; (d) or (d′) or (f′′) 2-bromobenzoic acid, EDC, DMAP, DCM, 3 h, 80%; (e′) or (e′′) 80% AcOH in H_2O, 65 °C, 12 h, 60%; (f′) R–Br [R = benzyl (**6a**), 4-methoxybenzyl (**6b**), methyl (**6c**)], NaH, DMF, 0 °C, 5–6 h, 85%; (d′′) BnBr, DCM : NaOH (aq.), TBAB, rt, 3 h, 80%.

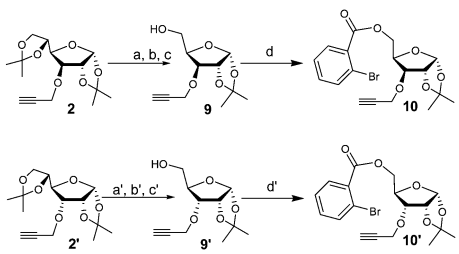
bis-electrophilic iodide or aldehyde (Madsen and Clausen) macrocyclization,[18,19] and (iv) Pd-catalyzed cross coupling.[20] In contrast, there are only a few reports of Sonogashira reaction being employed for the synthesis of such rings.[21–23] However, Pd-catalyzed ring annulations using carbohydrates for the synthesis of small sized oxygen and nitrogen containing bicyclic and tri-cyclic benzannulated molecular systems are well documented in recent literature.[24] Moreover, the carbohydrates have been used as "off-templates" for the stereoselective synthesis of chiral γ- and δ-lactones.[25–27] Interestingly, linking of carbohydrates to the reactive heterocycle increases water solubility, which is advantageous for bioavailability.[28] In continuation of our interest in synthetic benzannulated carbohydrate based macrocyclic ethers and thioethers[29] we therefore thought of applying similar strategy for the construction of carbohydrate based macrocyclic benzolactones. In this paper we demonstrate the feasibility of a modified form of Sonogashira reaction for the synthesis of unnatural chiral macrocyclic benzolactones (10, 11 and 12 membered rings) fused with furanose/pyranose sugars. In the process, we discovered a new non-lactonization strategy for the construction of macrocyclic benzolactones as elucidated herein.

We prepared the required scaffolds from simple, commercially available and cheap starting materials like diacetone glucose and D-glucal. In order to bring diversity in their structures, we utilized different positions of starting sugars, *viz.* 3–5, 3–6, 5–6 and 1–2 positions (Schemes 1–4).

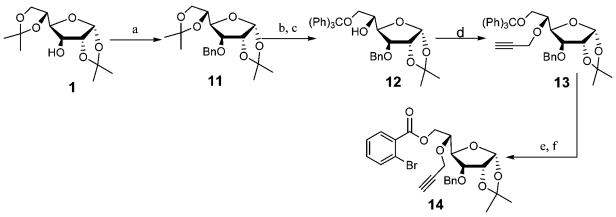
Utilizing 3–5 and 3–6 positions of sugar: Substrates **4**, **6** and **10** were synthesized using 3–5 positions of diacetone glucose (Schemes 1 and 2) while **8** was prepared using 3–6 positions (Scheme 1). The substrate **10′** was synthesized using 3–5 position of diacetone allose by doing a similar sequence reaction steps. Propargylation of **1** gave **2** which on deprotection of 5–6 isopropylidene unit followed by protection at primary alcoholic position (C-6 of sugar) gave intermediate **3**. This was then converted to **4a–c**, **6a–c** and **8** using suitable reaction sequences as detailed in Scheme 1. Intermediate **2** (from Scheme 1) was used for the preparation of **10** while the intermediate **2′** (Scheme 2) was prepared from diacetone allose by doing a similar sequence of reactions as that for **2**. Initial deprotection of 5–6 isopropylidene unit of **2** followed by $NaIO_4$ cleavage of the resulting diol led to the formation of an aldehyde which was subsequently reduced to alcohol **9**. Compound **9** was then subjected to EDC coupling with 2-bromobenzoic acid giving **10** (Scheme 2). Scaffold **10′** was prepared similarly using allose-derived intermediate **2′** instead of diacetone glucose (Scheme 2, for detailed procedures see ESI†).

Utilizing 5–6 position of sugar: Benzylation at 3-position of **1** followed by deprotection of 5–6 isopropylidene unit and then tritylation at primary OH of diol gave **12**. The intermediate was propargylated at 5-OH, detritylated and subjected to EDC coupling with 2-bromobenzoic acid to generate the scaffold **14** (Scheme 3, for detailed procedures see ESI†).

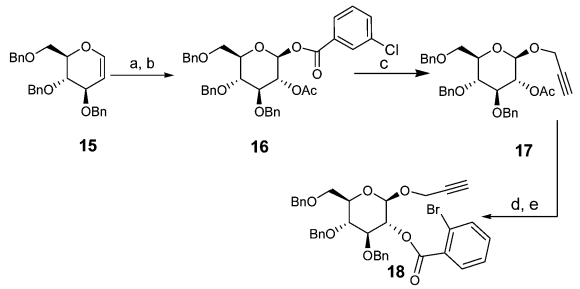
Utilizing 1–2 position of sugar: Tri-*O*-benzyl-D-glucal **15** was treated with *m*-CPBA and then acetylated to give **16**, which on propargylation at anomeric position gave **17**. This was then deacetylated at 2-position and submitted to EDC coupling to build the scaffold **18** (Scheme 4, for detailed procedures see ESI†).



Scheme 2 Substrates for Sonogashira reaction utilizing 3–5 position of sugar. *Reagents and conditions*: (a/a′) 70% AcOH in H_2O, rt, 8 h, 75%; (b/b′) silica supported $NaIO_4$, DCM, rt, 5 h, 91%; (c/c′) $NaBH_4$, MeOH, 0 °C, 0.5 h, 82%; (d/d′) 2-bromobenzoic acid, EDC, DMAP, DCM, rt, 3 h, 80%.



Scheme 3 Substrates for Sonogashira reaction utilizing 5–6 position of sugar. *Reagents and conditions*: (a) BnBr, DCM : NaOH (aq.), TBAB, rt, 3 h, 80%; (b) 70% AcOH in H_2O, rt, 8 h 75%; (c) trityl chloride, Py, 65%; (d) propargyl bromide, DCM : NaOH (aq.), TBAB, rt, 3 h, 80%; (e) 80% AcOH in H_2O, 65 °C, 12 h, 60% (detritylation); (f) 2-bromobenzoic acid, EDC, DMAP, DCM, rt, 3 h, 80%.

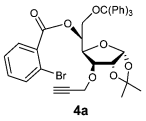
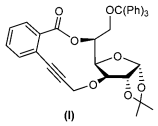
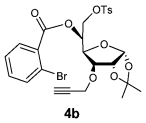
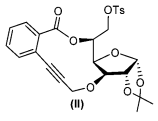
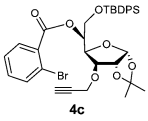
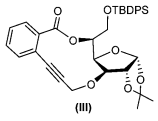
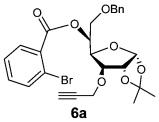
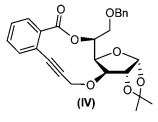
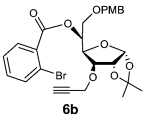
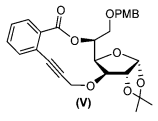
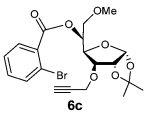
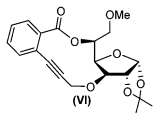
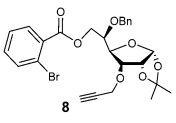
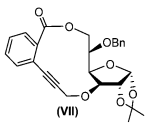
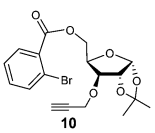
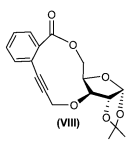
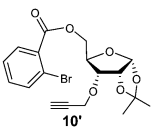
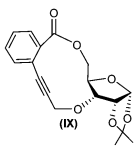
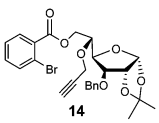
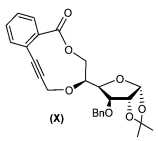
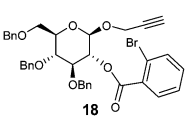
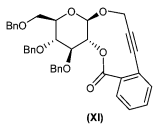


Scheme 4 Scaffolds for Sonogashira reaction utilizing 1–2 position of sugar. *Reagents & conditions*: (a) *m*-CPBA, $CHCl_3$, rt, 5–8 h, N_2 atm, 40%; (b) Ac_2O, Py, rt, 2 h, 95%; (c) propargyl alcohol, $BF_3 \cdot Et_2O$, 0 °C, 12 h, 78%; (d) NaOMe, MeOH, rt, 0.5 h, 95%; (e) 2-bromobenzoic acid, EDC, DMAP, DCM, rt, 3 h, 80%.

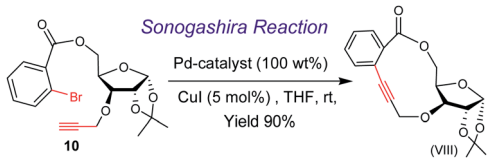
The substrates (**4**, **6**, **8**, **10**, **10′**, **14** and **18**) synthesized above, containing the required reactive sites (alkyne and aryl halide), were then cyclized giving macrocyclic benzolactones in 80–90% yield (entries 1–11, Table 1). The Pd-catalyst used in this reaction is an alumina supported heterogeneous catalyst (characterized in our previous communication, see ref. 29) containing basic sites on it so that there is no requirement of external base. Taking the scaffold **10** as a model substrate, we carried out the reaction using this Pd-catalyst (100 mg for 100 mg of substrate) and 5 mol% CuI as co-catalyst in dry THF (Scheme 5). The completion of reaction was checked by TLC which showed the complete consumption of starting material after about 25 hours giving **VIII** in 90% yield. The product was purified by column chromatography and fully characterized by ^{1}H and ^{13}C NMR spectroscopic data.

In the ^{1}H NMR spectrum of cyclization precursor **10**, the acetylenic proton signal appears at δ 2.44 ppm (encircled as B in Fig. 4) which is absent in the ^{1}H NMR spectrum of the cyclized product (**VIII**). The CH_2 proton signals of the propargyl group in **10** (Ha/Hb encircled as A in Fig. 4) appear as two double doublets at δ 4.24 and 4.28 ppm (due to geminal coupling as well as coupling with terminal C–H proton of propargyl group) overlapping a doublet-like signal at 4.22 ascribable to H-3, while in the spectrum of **VIII**, two doublet signals at δ 4.31 and 4.33 ppm (encircled as C in Fig. 4) are observed due to the absence of terminal C–H proton. Further, there is only one quaternary carbon signal between δ 70–80 ppm (at 78.8 ppm, encircled as D in Fig. 4) in the ^{13}C NMR spectrum of **10**, though that of **VIII**

Table 1 List of macrocyclic chiral benzolactones fused with sugars synthesized using Sonogashira reaction

Entry	Substrate[a]	Product[b]	Time (h)	Yield[c] (%)
1			25	85
2			20	81
3			22	87
4			25	88
5			20	83
6			24	80
7			25	89
8			25	90
9			25	82
10			20	85
11			23	86

[a] *Reaction conditions*: substrate (100 mg), Pd-catalyst (100 wt%), CuI (5 mol%), THF (3.0 mL), rt. [b] Characterized through spectroscopic analysis. [c] Isolated yields after column purification.



Scheme 5 Ring closure by intramolecular Sonogashira reaction.

showed two such signals (encircled as E in Fig. 4) at δ 70.9 and 74.8 ppm.

As an illustration of the utility of the present method, the synthesis of chiral macrocyclic benzolactones of the type **20** was taken up from easily available starting materials diacetone glucose and 2-bromobenzoic acid. The synthetic strategy involves the preparation of intermediate **9** from diacetone glucose followed by EDC coupling, Sonogashira coupling and $NaIO_4$ cleavage of the sugar moiety (Fig. 5).

The compound **VIII**, synthesized above (Schemes 2 and 5), was treated with TFA–H_2O (3 : 1) followed by $NaIO_4$ cleavage of the resulting sugar diol gave the di-aldehyde **19**, which was reduced with $NaBH_4$ giving benzolactone **20** in 50% yield over three steps as shown in Scheme 6 (for detailed procedures see ESI†).[30]

In summary, a modified form of Sonogashira coupling involving Pd-catalyst containing basic sites was successfully applied for the synthesis of 10, 11 and 12-membered chiral benzolactones fused with carbohydrates. The scaffolds required for the reaction were synthesized using conventional protection–deprotection strategies. The stereochemistry of the products was predefined due to the inherent chirality of

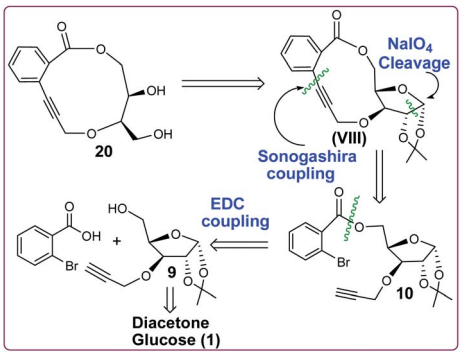


Fig. 5 Retrosynthetic analysis of benzolactone **20**.

carbohydrates. The method has been utilized for the synthesis of benzolactone **20**. The synthesized benzolactones (entries 1–11, Table 1) are under investigation for their anticancer and antimicrobial activities.

Experimental section

Unless otherwise stated, materials were obtained from commercial suppliers and were used without further purification. All reactions were performed under nitrogen atmosphere unless stated otherwise. TLC was performed on pre-coated silica gel plates (F254, 0.25 mm thickness); compounds were visualized by charring with ceric ammonium sulphate–H_2SO_4 system or using UV light. ^1H and ^{13}C NMR spectra were recorded on 400 MHz and 125 MHz spectrometers respectively. Chemical shifts (δ) are quoted in ppm and are referenced to TMS as internal standard. Removal of solvent *in vacuo* refers to distillation using

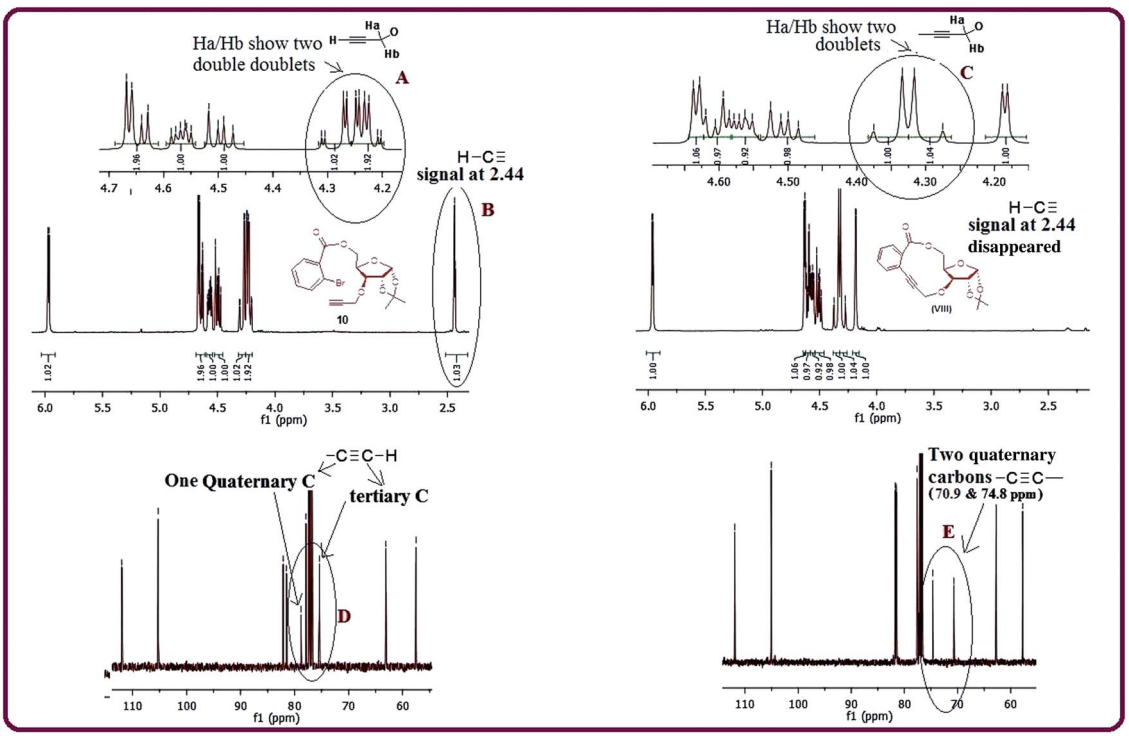
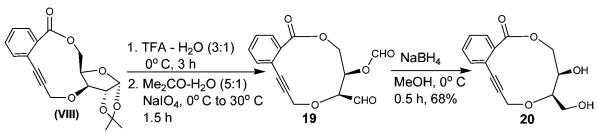


Fig. 4 Selected regions of spectra of cyclization precursor (**10**) and cyclized product (**VIII**).



Scheme 6 Synthesis of benzolactone **20** using the present methodology.

a rotary evaporator attached to an efficient vacuum pump. Products obtained as solids or syrups were dried under high vacuum. Solvents used were mainly of LR grade and for reactions dry solvents were used purchased from Sigma Aldrich. Optical rotation measurements were carried out on Perkin-Elmer 241 polarimeter.

Typical procedure for cyclization *via* intramolecular Sonogashira reaction: synthesis of compound VIII

The cyclization precursor **10** containing alkynyl group and aryl halide moiety (100 mg, 0.24 mmol) was dissolved in dry THF (3.0 mL). Heterogeneous Pd-catalyst R (reported in our previous paper ref. 29) containing basic support (100 wt%) and co-catalyst CuI (5 mol%) were added to the above solution and the reaction mixture was allowed to stir for several hours at room temperature under nitrogen environment. After ascertaining completion of the reaction by TLC, the catalyst was filtered and the solvent was evaporated under vacuum. The reaction mixture was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. After evaporation, the product was purified by column chromatography on silica gel using petroleum ether–ethyl acetate as the eluent to obtain the pure product **VIII** as a thick liquid (72.3 mg, 90%); Rf (45% EtOAc/hexane) 0.50; $[\alpha]_D^{25}$ −1.30° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 2980, 2938, 2210, 1733, 1588 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (dd, $J = 7.4$, 2.0 Hz, 1H), 7.66 (dd, $J = 7.7$, 1.2 Hz, 1H), 7.44–7.27 (m, 2H), 5.96 (d, $J = 3.7$ Hz, 1H), 4.63 (d, $J = 3.7$ Hz, 1H), 4.62–4.58 (m, 1H), 4.56 (dd, $J = 7.0$, 3.6 Hz, 1H), 4.50 (dd, $J = 10.1$, 6.0 Hz, 1H), 4.35 (d, $J = 16.5$ Hz, 1H), 4.30 (d, $J = 16.5$ Hz, 1H), 4.18 (d, $J = 2.9$ Hz, 1H), 1.51 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 134.4, 132.7, 131.7, 131.6, 127.2, 121.9, 112.1, 105.2, 81.9, 81.7, 76.8, 74.8, 70.9, 62.9, 57.9, 26.8, 26.3; ESI MS (*m*/*z*): 330 [M^+]; Anal. calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found C, 65.35; H, 5.38%.

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