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Rapid access to the synthesis of polysubstituted δ-lactones via tandem stereoselective conjugate addition/α-alkylation of unsaturated 7,3-lactone-α-D-xylofuranose derivative

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ABSTRACT

α-D-*xylo*-7,3-Unsaturated lactone, a versatile chiral building block, undergoes Cu-catalyzed conjugated addition with high yield and stereoselectivity. When the conjugated reaction is quenched with a suitable alkyl halide, a tandem stereoselective conjugated/α-alkylation reaction is achieved. Further, selective hydrolysis of the 1,2-*O*-isopropylidene moiety followed by oxidative cleavage and reduction reaction, afforded the title compounds.

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Conjugate addition (sometimes known as the Michael addition), probably represents the best way for introducing a nucleophile in the β-position of an unsaturated carbonyl compound.[1] As this nucleophilic introduction affords an incipient enolate intermediate, the chemical reaction can be quenched by a suitable electrophile and thus turns this reaction into a sequential or tandem transformation that, not only allows the incorporation of two functional groups during the same chemical transformation, but can also be done under enantio-and diastereoselective fashion.[2] Regarding the diastereoselective conjugated addition (DCA),[3] the use of chiral auxiliary[4] and chiral substrates[5] have proven to be two powerful tools which provide optical purity at low cost; especially if the source of chirality comes from carbohydrates (chiral pool).

During the course of a project designed to synthesize biologically important lactones, the preparation of novel optically pure polysubstituted δ-lactones was required; those by the way, are common fragments in many biologically important compounds (Fig. 1).[6] For that reason, we report here a rapid and efficient methodology for the synthesis of the required lactones based on the DCA-and the tandem DCA/α-alkylation reaction by taking advantage of the chiral substrate approach.[5,8] To this end, a DCA reaction

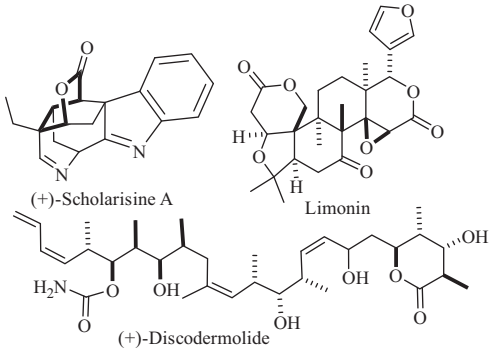

Figure 1. Biological important compounds containing the polysubstituted δ-lactone fragment.[7]

of the unsaturated 7,3-δ-lactone-α-D-xylofuranose derivative **1** was planned. Once the DCA methodology is set up, we will try to trap the enolate intermediate with alkyl halides to thus developing a tandem DCA/α-alkylation reaction.

Finally, by conducting a selective hydrolysis of the 1,2-*O*-isopropyliden moiety of the DCA/α-alkylation products, followed by oxidative cleavage of the respective 1,2-diols; and the reduction of the formed dicarbonyl compounds with $NaBH_4$, the required polysubstituted δ-lactones will be obtained (Fig. 2). This simple strategy may result to be attractive because the preparation of the chiral

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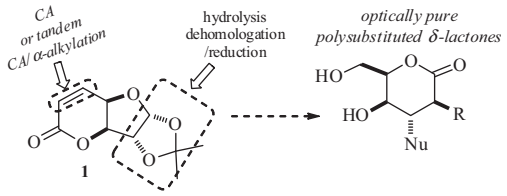


Figure 2. Strategy for the synthesis of polysubstituted lactones.

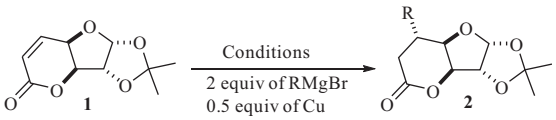
synton **1** is rapidly achieved (in multi gram-scale) from diacetone-D-glucose in a sequential hydrolysis–oxidation–Wittig olefination (SHOWO protocol[9]) featuring a highly diastereoselective Wittig olefination reaction in aqueous media.[9c]

Because the high efficiency of the Cu-catalyzed DCA of Grignard reagents to α,β-unsaturated esters (and related compounds) is well recognized;[3a] the present work begins with the treatment of lactone **1** with of *p*-F-PhMgBr and $CuBrSMe_2$. The use of higher amounts of Cu catalyst or Grignard reagent (e.g., 10 equiv of RMgBr and 5 equiv of $CuBrSMe_2$),[10] as well as additional additives (TMSCl, LiBr, HMPA)[11] was not necessary, since only 0.5 equiv of $CuBrSMe_2$ and 2 equiv of the Grignard reagent at −40 °C was more than enough to obtain high yield and high *anti*-stereoselectivity (see entries 1 and 2).[12]

The use of CuI as catalyst was less effective than $CuBrSMe_2$ (entry 3); therefore the $CuBrSMe_2$ catalyst was used for the other experiments. With ethyl, methyl and benzyl Grignard reagents (entries 4–6) the DCA products were obtained with high yields (75–85%) and stereoselectivity (96%); however, only 8% yield of the DCA product was obtained for the case of allylMgCl (entry 7), or only a trace was observed when CuI was used (entry 8). In these two latter cases, the 1,2-addition compound (not shown) was obtained as the major product (Table 1).

Having set up an efficient protocol for the DCA of lactone **1**, we then focused on the tandem protocol. Thus, the reaction mixture of DCA (with *p*-F-PhMgBr and BnMgCl as Grignard reagents, and CuBrSMe as catalyst) at −40 °C was treated with selected alkyl halides (CH_3I, BnBr, and allyliodide) and stirred at room temperature for 3 h.[13] The expected α-alkylation proceeded with moderated yields (63–70%); however, only one stereoisomer was isolated after chromatographic purification (Table 2). The analysis of representative coupling constants and selected 2D-NOESY interactions of lactone **4** (R_1 = *p*-F-Phenyl, R_2 = allyl) indicates that both substituents are *trans*-oriented with a boat-twisted conformation **4T** for the δ-lactone ring (Fig. 3). The large value of vicinal coupling constant ($^3J_{H5\text{-}H6}$ = 12.0 Hz), and the smaller $^3J_{H4\text{-}H5}$ value (3.9 Hz) confirms

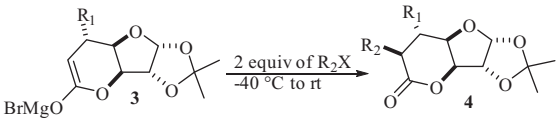
Table 1
Diastereoselective conjugated addition (DCA) to lactone **1**



Entry	RMgX		Yield (%)	de (%)
1	*p*-F-PhMgBr	$CuBrSMe_2$, THF at 0 °C	78	80
2	*p*-F-PhMgBr	$CuBrSMe_2$, THF at −40 °C	88	97
3	*p*-F-PhMgBr	CuI, THF at 0 °C	52	90
4	EtMgBr	$CuBrSMe_2$, THF at −40 °C	85	96
5	CH_3MgBr	$CuBrSMe_2$, THF at −40 °C	75	96
6	BnMgCl	$CuBrSMe_2$, THF at −40 °C	82	96
7[a]	AllylMgCl	$CuBrSMe_2$, THF at −40 °C	8	—
8[a]	AllylMgCl	CuI, THF at −40 °C	Trace	—

[a] 1,2-Addition compared as major product.

Table 2
Stereoselective α-alkylation of enolate **3**



Entry	R_1	R_2X	Yield[a] (%)
1	*p*-F-Ph	CH_3I	65
2	*p*-F-Ph	BnBr	63
3	*p*-F-Ph	Allyliodide	68
4	Bn	Allyliodide	63

[a] Yields after chromatographic purification.

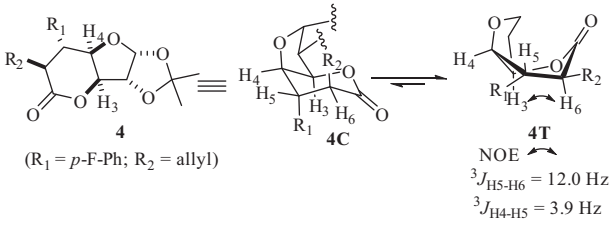
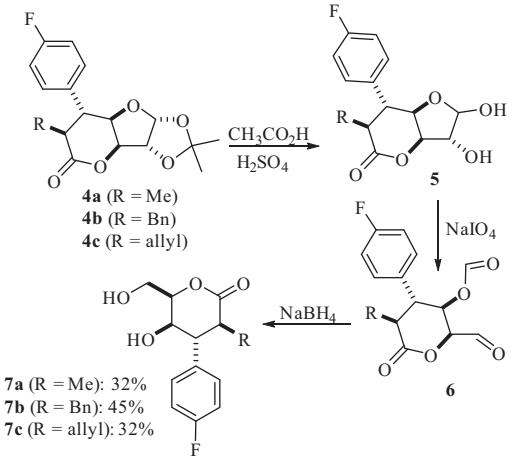


Figure 3. Stereochemistry and conformational preference of δ-lactone **4**.

the *anti*-relationship between H5 and H6 and the pseudo diequatorial relationship between H4 and H5, respectively. Because all of the δ-lactones possess very similar coupling constants, it can be assumed that all of them enjoy the same major conformation **4T**. The stereochemical outcome of α-alkylation of the enolates is consistent with models previously proposed either in cyclic or acyclic systems.[2,14]

We finally proceeded to transform the δ-lactones **4a**–**c** into the desired polysubstituted δ-lactones **7a**–**c**. Selective hydrolysis of the 1,2-*O*-isopropyliden moiety with a mixture of acetic acid/sulfuric acid at room temperature afforded the respective 1,2-diols **5** which were treated with an aqueous solution of $NaIO_4$ at 0 °C to obtain the dicarbonyl compounds **6**, and finally, with the reduction of **6** with $NaBH_4$, the polysubstituted δ-lactones **7** were prepared in modest overall yields (Scheme 1).[15]



Scheme 1. Preparation of polysubstituted δ-lactones.

In conclusion, a fast and accessible stereoselective protocol was developed for the preparation of optically pure polysubstituted δ-lactones[16] featuring a tandem diastereoselective conjugated addition/α-alkylation reaction. Applications of this methodology to the synthesis of biologically active lactones are in progress.

Acknowledgments

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12. *General procedure for the conjugate addition.* A mixture of Grignard reagent solution (0.94 mmol) and copper (I) bromide–dimethyl sulfide complex (48.3 mg, 0.24 mmol) was stirred at room temperature for 1 h. Then, lactone **1** (100.0 mg, 0.47 mmol) dissolved in dried THF (3 mL) was added to the reaction mixture at −40 °C. The resulting mixture was stirred for 3 h. After the reaction was completed, the reaction mixture was quenched with a saturated solution of ammonium chloride, and extracted with EtOAc (3 × 20 mL). The residue was purified through column chromatography (silica, eluent: mixture of hexane and ethyl acetate).
2 *(R = Me):* as a yellow syrup, 80.5 mg (75%). $[\alpha]^{25}$ +16.0 ($CHCl_3$, *c* 1.0). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.16 (d, *J* = 7.6 Hz, 1H), 1.34 (s, 3H), 1.52 (s, 3H), 2.25 (dd, *J* = 16.8, 5.2 Hz, 1H), 2.41 (m, 1H), 2.77 (dd, *J* = 16.8, 5.2 Hz, 1H), 4.25 (t, *J* = 3.3 Hz, 1H), 4.72 (m, 2H), 5.95 (d, *J* = 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 17.9, 26.2, 26.6, 28.7, 32.9, 77.5, 81.9, 83.8, 104.8, 112.2, 169.2. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{11}H_{16}O_5$ 228.0998; found 228.1027.
2 *(R = Et):* as a yellow syrup, 96.8 mg (85%). $[\alpha]^{25}$ +17.2 ($CHCl_3$, *c* 1.0). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.03 (t, *J* = 7.6 Hz, 3H), 1.34 (s, 3H), 1.52 (m, 3H), 1.25–1.60 (m, 2H), 2.14 (m, 1H), 2.26 (dd, *J* = 16.8, 6.8 Hz, 1H), 2.71 (dd, *J* = 16.8, 5.6 Hz, 1H), 4.31 (t, *J* = 3.6 Hz, 1H), 4.66 (d, *J* = 3.2 Hz, 1H), 4.73 (d, *J* = 4.0 Hz, 1H), 5.95 (d, *J* = 3.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 11.4, 25.8, 26.2, 26.6, 26.7, 31.4, 35.9, 76.6, 82.0, 83.6, 104.7, 112.1, 169.8. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{18}O_5$ 242.1154; found 242.1119.
2-(R = p-F-phenyl): as a yellow syrup, 127.5 mg (88%). $[\alpha]^{25}$ −4.7 ($CHCl_3$, *c* 1.0). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.32 (s, 3H), 1.47 (s, 3H), 2.70 (dd, *J* = 16.8, 6.6 Hz), 2.99 (dd, *J* = 16.8, 6 Hz, 1H), 3.52 (q, *J* = 6.0, 4.2 Hz, 1H), 4.46 (t, *J* = 3.6 Hz, 1H), 4.61 (d, *J* = 3.0 Hz, 1H), 4.75 (d, *J* = 3.9 Hz, 1H), 6.01 (d, *J* = 3.6 Hz, 1H), 7.06 (m, 2H), 7.21 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 26.1, 26.5, 31.3, 39.1, 78.4, 81.8, 83.5, 104.9, 112.3, 116.2 (d, *J* = 20.6 Hz), 128.5 (d, *J* = 8.0 Hz), 135.1 (d, *J* = 3.4 Hz), 162.1 (d, *J* = 246 Hz), 169.3. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{17}FO_5$ 308.1060; found 308.1075.
2 *(R = Bn):* as a yellow syrup, 117.3 mg (82%). $[\alpha]^{25}$ +2.6 ($CHCl_3$, *c* 1.0). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.33 (s, 3H), 1.47 (s, 3H), 2.26 (dd, *J* = 16.8, 5.2 Hz, 1H), 2.54–2.69 (m, 3H), 2.89 (dd, *J* = 12.8, 5.6 Hz, 1H), 4.35, (dd, *J* = 3.2, 3.2 Hz, 1H), 4.34 (d, *J* = 3.6 Hz, 1H), 4.75 (d, *J* = 3.2 Hz, 1H), 5.95 (d, *J* = 3.6 Hz, 1H), 7.15–7.34 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 26.2, 26.6, 30.6, 35.9, 38.7, 76.2, 82.0, 83.8, 104.6, 112.3, 126.9, 128.8, 137.4, 169.3. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{17}H_{20}O_5$ 304.1311; found 304.1341.
2 *(R-allyl):* as a yellow syrup, 9.5 mg (8%). $[\alpha]^{25}$ +3.0 ($CHCl_3$, *c* 0.7). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.34 (s, 3H), 1.51 (s, 3H), 2.15–2.35 (m, 4H), 2.71 (dd, *J* = 15.9, 4.8 Hz, 1H), 4.32 (dd, *J* = 3.3, 3.3 Hz, 1H), 4.67 (d, *J* = 3.0 Hz, 1H), 4.73 (d, *J* = 3.9 Hz, 1H), 5.12 (dm, *J* = 8.1 Hz, 1H), 5.17 (br s, 1H), 5.75 (m, 1H), 5.94 (d, *J* = 3.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 26.2, 26.6, 29.7, 31.1, 33.7, 36.9, 76.4, 81.9, 83.7, 104.6, 112.3, 118.6, 133.8, 169.4.
13. *General procedure for the tandem conjugate addition/α-alkylation.* A mixture of Grignard reagent solution (0.94 mmol) and copper (I) bromide–dimethyl sulfide complex (0.24 mmol) was stirred at room temperature for 1 h. Then, a solution of lactone **1** (100.0 mg, 0.47 mmol) in dried THF (3 mL) at −40 °C was added to the reaction mixture. The resulting mixture was stirred for 3 h before adding the respective alkyl halide (1.41 mmol). The reaction mixture was warmed to room temperature and stirred for 2.5 hours. The reaction mixture was quenched with a saturated solution of ammonium chloride, and extracted with EtOAc (3 × 20 mL).
4 *(R_1 = p-F-Ph, R_2 = Me):* as a white solid, 90.9 mg (60%). Mp = 145 °C. $[\alpha]^{25}$ +41.9 ($CHCl_3$, *c* 1.0). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.0 (d, *J* = 6.6 Hz, 1H), 1.32 (s, 3H), 1.43 (s, 3H), 2.60 (m, 1H), 2.85 (dd, *J* = 12.9, 4.5 Hz, 1H), 4.56 (dd, *J* = 3.9, 3.3 Hz, 1H), 4.78 (d, *J* = 3.0 Hz, 1H), 4.82 (d, *J* = 3.9 Hz, 1H), 5.97 (d, *J* = 3.6 Hz, 1H), 7.08 (m, 2H), 7.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 13.55, 26.06, 26.5, 38.7, 48.5, 80.7, 82.3, 83.0, 104.6, 112.2, 116.1 (d, *J* = 21.7 Hz), 129.2 (d, *J* = 9.1 Hz), 136.4 (d, *J* = 3.4 Hz), 162.1 (d, *J* = 244.8 Hz), 173.2. HRMS-EI (*m*/*z*): [M]+ calcd for $C_{17}H_{19}FO_5$ 322.1217; found 322.1179.
4 *(R_1 = p-F-Ph, R_2 = Bn):* as a yellow syrup, 112.3 mg, (60%). $[\alpha]^{25}$ +55.8 ($CHCl_3$, *c* 1.1). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.31 (s, 3H), 1.42 (s, 3H), 2.63 (dd, *J* = 14.0, 4.0 Hz, 1H), 2.86 (m, 1H), 3.08 (m, 2H), 4.50 (t, *J* = 3.6 Hz, 1H), 4.74 (d, *J* = 2.8 Hz, 1H), 4.79 (d, *J* = 4.0 Hz, 1H), 5.97 (d, *J* = 3.6 Hz, 1H), 7.06 (m, 4H), 7.14 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 26.0, 26.5, 34.3, 46.0, 80.7, 81.5, 83.0, 104.6, 112.2, 116.2 (d, *J* = 21.3 Hz), 126.4, 128.3, 129.2, 129.4 (d, *J* = 7.5 Hz), 136.3 (d, *J* = 3.4 Hz), 139.1, 162.1 (d, *J* = 244.9 Hz), 172.1. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{23}H_{23}FO_5$ 398.1530; found 398.1492.
4-(R_1 = p-F-Ph, R_2 = allyl): as a yellow syrup, 106.4 mg (65%). $[\alpha]^{25}$ +38.2 ($CHCl_3$, *c* 1.1). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.32 (s, 3H), 1.42 (s, 3H), 2.18 (m, 1H), 2.30 (m, 1H), 2.67 (m, 1H), 3.07 (dd, *J* = 12.0, 3.9 Hz, 1H), 4.50 (t, *J* = 3.6 Hz, 1H), 4.77 (d, *J* = 2.7 Hz, 1H), 4.80 (d, *J* = 3.9 Hz, 1H), 4.85 (dm, *J* = 17.4 Hz, 1H), 5.01 (dm, *J* = 10.2 Hz, 1H), 5.80 (m, 1H), 5.96 (d, *J* = 3.6 Hz, 1H), 7.07 (m, 2H), 7.17 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 26.0, 26.4, 31.9, 43.1, 45.2, 80.6, 82.0, 83.0, 104.5, 112.2, 116.0 (d, *J* = 21.6 Hz), 118.2, 129.3 (d, *J* = 7.9 Hz) 134.0, 136.1 (d, *J* = 3.4 Hz), 162.1 (d, *J* = 246.0 Hz), 172.0. HRMS-FAB (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{21}FO_5$ 348.1373; found 348.1402.
4 *(R_1 = Bn, R_2 = allyl):* as a yellow syrup, 97 mg (60%). $[\alpha]^{25}$ +14.5 ($CHCl_3$, *c* 1.0). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.29 (s, 3H), 1.39 (s, 3H), 2.34 (dd, *J* = 13.2, 6.0 Hz, 1H), 2.50 (m, 2H), 2.64 (dd, *J* = 13.8, 8.7 Hz, 1H), 2.90 (dd, *J* = 13.5, 6.3 Hz, 1H), 4.32 (t, *J* = 2.4 Hz, 1H), 4.62 (d, *J* = 2.4 Hz, 1H), 4.69 (d, *J* = 3.9 Hz, 1H), 5.09 (br s, 1H), 5.14 (dm, *J* = 5.7 Hz, 1H), 5.72 (m, 1H), 5.83 (d, *J* = 3.9 Hz, 1H), 7.17 (m, 2H), 7.29 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 26.3, 26.4, 34.4, 37.7, 38.6, 41.6, 76.3, 80.5, 83.2, 104.2, 112.3, 118.1, 127.0, 128.7, 129.2, 134.6, 137.4, 172.0.
14. Shintani, R.; Tokunaga, N.; Doi, H.; Hayashi, T. *J. Am. Chem. Soc.* **2004**, *126*, 6240.
15. To a solution (3 mL) made of a mixture of acetic acid (46%), sulfuric acid (16%), and water (38%) was added therespective lactone **4** (0.31 mmol) and allowed to react for 2.5 h (monitored by tlc) at room temperature. Then, the reaction mixture was neutralized with a saturated solution of sodium carbonate and extracted with EtOAc (3 × 20 mL). The organic phase was concentrated under the reduced pressure and dissolved in THF (2 mL), and sodium periodate (0.4 mmol) was added. The reaction mixture was stirred for 40 min, and the formed solids were filtered and the organic phase was concentrated under reduced pressure giving the respective aldehyde **6** as a yellow oil. Compound **6** was dissolved in THF (2 ml) and H_2O (0.5 mL) and sodium borohydride (0.46 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h before adding water (1 mL), and the THF was evaporated under reduced pressure and the residue was extracted with ethyl acetate (3 × 20 ml). The organic phase was evaporated and the residue was purified by chromatography on silica gel (hexane/ethyl acetate).
Compound ***7a****:* as a colorless liquid, 32%, $[\alpha]^{25}$ −84.5 ($CHCl_3$, *c* 0.9). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 1.22 (d, *J* = 6.9 Hz, 3H), 3.40 (m, 2H), 3.55 (m, 2H), 3.69 (dd, *J* = 11.1, 7.5 Hz, 1H), 4.53 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.08 (m, 2H), 7.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 14.2, 38.1, 51.8, 63.9, 69.6, 80.4, 115.9 (d, *J* = 20.5 Hz), 129.9 (d, *J* = 7.9 Hz), 130 (d, *J* = 3.37 Hz), 162.2 (d, *J* = 246.0 Hz), 179.7.
Compound ***7b****:* As a yellow liquid (45%). $[\alpha]^{25}$ −76.2 ($CHCl_3$, *c* 1.0). ^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 2.94 (dd, *J* = 14.0, 5.2 Hz, 1H), 3.01 (dd, *J* = 14.0, 5.2 Hz, 1H), 3.35 (dd, *J* = 7.2, 4.4 Hz, 1H), 3.54 (m, 2H), 3.68 (m, 2H), 4.37 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.02 (m, 4H), 7.20 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 14.2, 34.1, 44.5, 47.6, 63.9, 69.7, 80.4, 115.6 (d, *J* = 20.5 Hz), 126.7, 128.4, 129.7, 130.1 (d, *J* = 7.9 Hz), 130.6, 137.0, 162.1 (d, *J* = 245.8 Hz), 178.2. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{19}FO_4$ 330.1267; found 330.1245.

Compound **7c**: As a yellow liquid (40%). $[\alpha]^{25}$ −76.7 ($CHCl_3$, *c* 1.0). $_1$H NMR (400 MHz, $CDCl_3$) δ: 2.39 (m, 1H), 2.49 (m, 1H), 3.40 (m, 1H), 3.46 (m, 1H), 3.58 (m, 1H), 3.69 (m, 1H), 4.50 (d, *J* = 8.4 Hz, 1H), 4.99 (d, *J* = 8.4 Hz, 1H), 5.03 (br s, 1H), 5.55 (m, 1H), 7.06 (t, *J* = 8.6 Hz, 2H), 7.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 32.9, 43.0, 48.2, 63.9, 69.7, 80.5, 115.81 (d, *J* = 21.2 Hz), 118.6, 130.1 (d, *J* = 7.6 Hz), 130.80 (d, *J* = 3.1 Hz), 133.5, 162.2 (d, *J* = 244.4 Hz), 178.2. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{17}FO_4$ 280.1111; found 380.1144.

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