Note

Electrophilic Cyclization and Intermolecular Acetalation of 2-(4-hydroxybut-1-yn-1-yl)benzaldehydes: Synthesis of Diiodinated Diepoxydibenzo[c,k][1,9]dioxacyclohexadecines

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Electrophilic Cyclization and Intermolecular Acetalation of 2-(4-hydroxybut-1-yn-1-yl)benzaldehydes: Synthesis of Diiodinated Diepoxydibenzo[*c*,*k*][1,9]dioxacyclohexadecines

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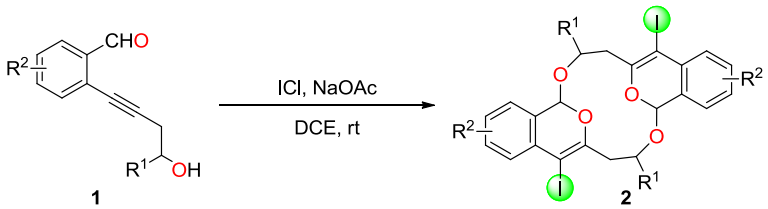
ABSTRACT

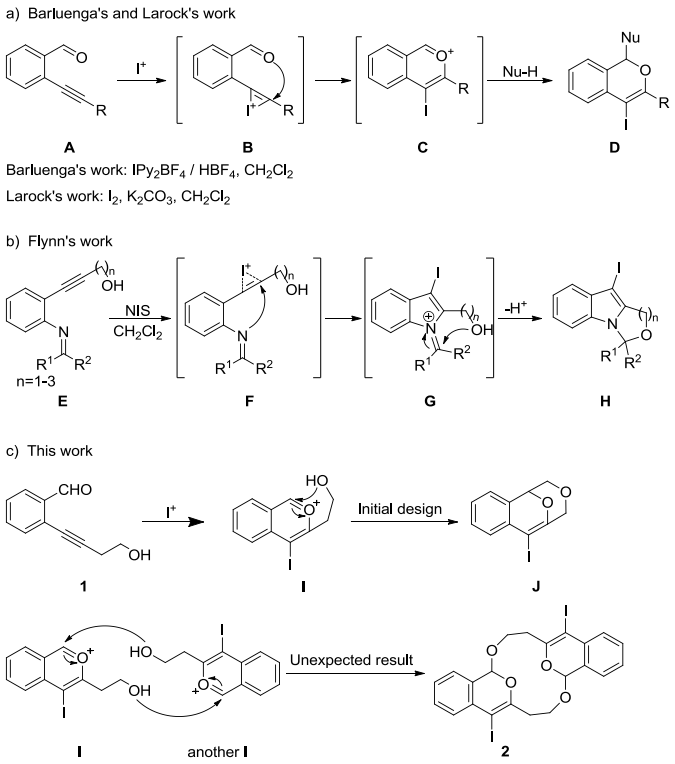


An expedient strategy for the preparation of diiodinated diepoxydibenzo[*c*,*k*][1,9]dioxacyclohexadecines from readily available 2-(4-hydroxybut-1-yn-1-yl)benzaldehydes through electrophile-triggered tandem cyclization/intermolecular acetalation sequence has been presented. The electrophilic macrocyclization can be performed under mild conditions and up to gram quantities. Moreover, palladium-catalyzed coupling and reduction reactions of the resulting iodides could efficiently afford oxa-macrocycles.

Macrocyclic polyethers acted as a special type of compounds have found

versatile applications in material science,[1] environmental science,[2] bioscience,[3] scientific energy,[4] and pharmacology.[5] Macrocyclic polyethers have played important roles in phase-transfer catalysis[6] and metal complex.[7] Moreover, macrocyclic polyethers continue to emerge in diverse fields, not only are common in antibiotic,[8] antitumoral[9] and protein,[10] but also are exploited in coordination chemistry[11] and supramolecular chemistry.[12] As applications of macrocyclic polyethers and their derivatives across many fields, the efficient strategies for the synthesis of macrocycles have been the focus of considerable attention for organic chemists and medicinal chemists. Within the quest for innovative strategies toward multifarious macrocyclic polyethers, a variety of effective methods have been explored. Usually, the methods for gaining access to macrocyclic polyethers involve Williamson's reaction,[13] ring-closing metathesis (RCM),[14] Pd-catalyzed cross-coupling[15] and activation of C-H bonds.[16] Although significant progress has been achieved for the synthesis of macrocyclic polyethers, the need for alternative methods is indeed desirable. Recently, electrophilic iodocyclization has emerged as a powerful method to construct a variety of functionalized carbocycles[17] and heterocycles.[18] The iodocyclizations are conducted under mild conditions, metal-free and environmentally friendly. Although great achievements have been made with respect to iodocyclization, few examples to prepare macrocyclic polyethers based on sequential cascade iodocyclizations have been reported until now.

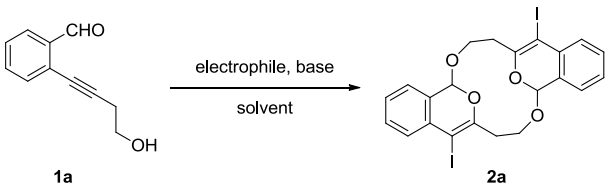
Scheme 1. Iodine-promoted Cascade Carbocyclization



In recent years, methods involving iodonium-induced activation of alkyne have provided the opportunity for preparing iodinated 1*H*-isochromene by Barluenga[19] and Larock[20] (Scheme 1a). This reaction is generally believed that the reactive species **B** activated by iodide cation was attacked by the oxygen of the carbonyl group to give the intermediate **C**. Subsequently, the pyrilium intermediate **C** is immediately trapped by the nucleophile to give the product **D**. In 2013, Flynn's group reported another analogous electrophilic cyclization to form ring-fused indoles (Scheme 1b).[21] The *N*-(2-alkynylphenyl)imines **E** underwent similar iodocylization to an imminum ion **G**, which was trapped by a nucleophile tethered to the alkynyl group to give **H**. Encouraged by these achievements and continuing our interest in iodocyclization, we envisioned that the substrates **1** containing a homopropargylic alcohol moiety could

undergo a similar iodocyclization to form the important intermediate **I**, which could go through the intramolecular cyclization to obtain the compound **J** (Scheme 1c). To our surprise, the intermediate **I** underwent the intermolecular acetalation rather than the intramolecular cyclization due to the ring strain (Scheme 1c). Herein, we report an effective method for the synthesis of diiodinated macrocyclic polyethers via cascade iodocyclization.

Table 1. Optimization Studies for the Synthesis of 2a[a]



1a 2a

entry	solvent	electrophile (equiv)	base (equiv)	yield[b] (%)
1	DCE	I_2 (1.0)	NaOAc (1.0)	23
2	DCE	NIS (1.0)	NaOAc (1.0)	trace
3	DCE	IBr (1.0)	NaOAc (1.0)	35
4	DCE	ICl (1.0)	NaOAc (1.0)	48
5	DCE	ICl (1.0)	NaOAc (1.5)	60
6	DCE	ICl (1.0)	NaOAc (2.0)	70
7	DCE	ICl (1.0)	NaOAc (2.5)	65
8	**DCE**	**ICl (1.2)**	**NaOAc (2.0)**	**75**
9	DCE	ICl (1.5)	NaOAc (2.0)	68
10	CH_2Cl_2	ICl (1.2)	NaOAc (2.0)	45
11	CH_3CN	ICl (1.2)	NaOAc (2.0)	26

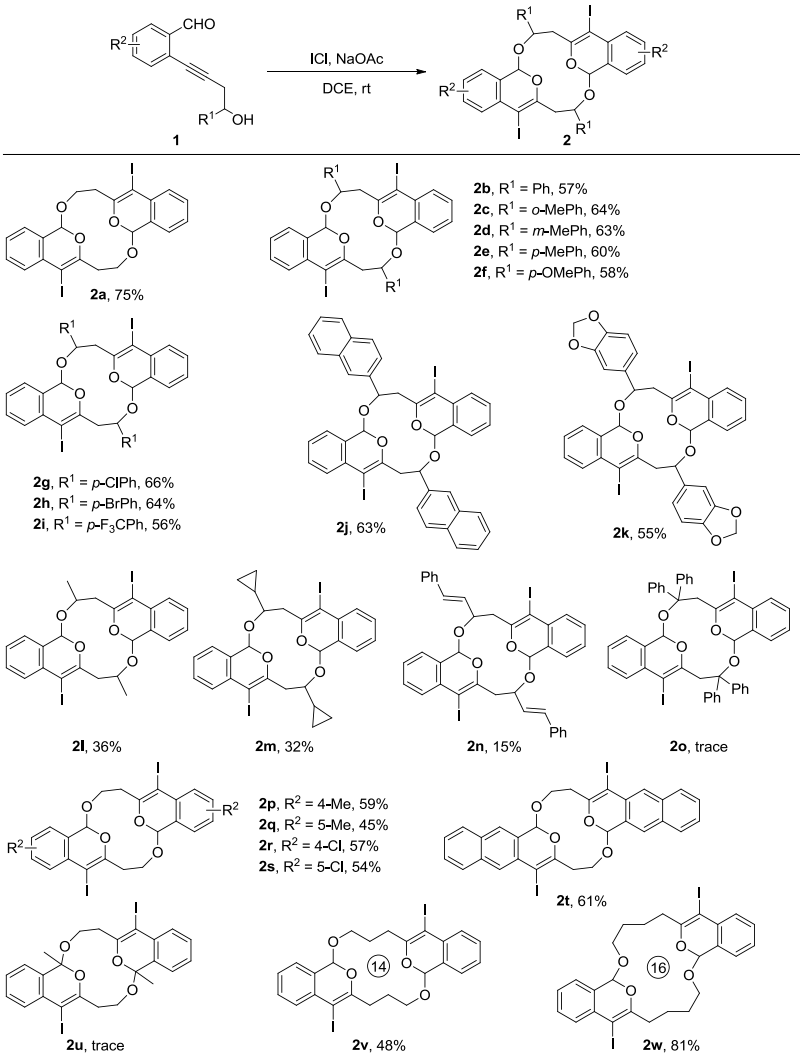
12	THF	ICl (1.2)	NaOAc (2.0)	36
13	acetone	ICl (1.2)	NaOAc (2.0)	18
14	toluene	ICl (1.2)	NaOAc (2.0)	trace
15	DCE	ICl (1.2)	K_2CO_3 (2.0)	66
16	DCE	ICl (1.2)	K_3PO_4 (2.0)	70
17	DCE	ICl (1.2)	^{t}BuOK (2.0)	trace
18	DCE	ICl (1.2)	NaOAc (2.0)	53[c]
19	DCE	ICl (1.2)	NaOAc (2.0)	61[d]

[a]All reactions were run under the following conditions, unless otherwise indicated: 0.20 mmol of **1a** and 1.2 equiv of electrophile in 4 mL of solvent were stirred at room temperature for 1 h. [b]Yields of isolated products. [c]The reaction was run in 6 mL DCE. [d]The reaction was run in 2 mL DCE.

At the onset of our investigation, we examined the reaction of 2-(4-hydroxybut-1-yn-1-yl)benzaldehyde (**1a**) with 1.0 equiv of I_2, 1.0 equiv NaOAc in 1,2-dichloroethane (DCE) (4 mL) at room temperature. The unexpected product **2a** was isolated in 23% yield after 1 h (Table 1, entry 1). After screening common electrophiles such as NIS, IBr and ICl, we found that the electrophile ICl was better than others (entries 1-4). When we adjusted the amount of NaOAc, the 2.0 equiv NaOAc was best for this reaction (entries 5-7). By increasing the amount of ICl to 1.2 equiv, the product **2a** was obtained in 75% yield (entry 8). Further increasing the amount of ICl to 1.5 equiv, a lower yield of **2a** was received (entry 9). Subsequently, when different solvents involving

CH_2Cl_2, CH_3CN, THF, acetone and toluene were studied, no better results were obtained (entries 10-14). After screening a series of bases such as NaOAc, K_2CO_3, K_3PO_4, and ^tBuOK, we found that NaOAc was the best (entries 8 and 15-17). In addition, no satisfactory yields were obtained when the reactions were carried out in diluted or concentrated conditions (entries 18-19). From the series of detailed investigations mentioned above, the combination of 1.0 equiv of **1a**, 1.2 equiv of ICl, and 2.0 equiv of NaOAc in DCE at room temperature for 1 h was determined as the optimum reaction conditions.

Table 2. Synthesis of Diiodinated Macrocyclic Polyethers of 2[a]



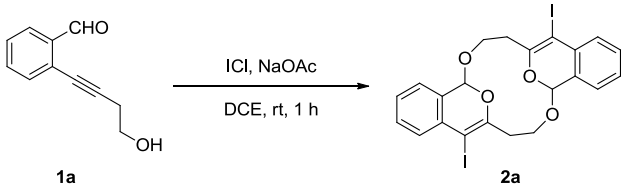
[a]All reactions were run under the following conditions, unless otherwise indicated: 0.20 mmol of **1** and 1.2 equiv of ICl in 4 mL of DCE were stirred at room temperature for 1 h. Yields are given for isolated products.

To investigate the generality and the scope of this reaction, various 2-(4-hydroxybut-1-yn-1-yl)benzaldehyde derivatives were subjected to the above mentioned conditions, as summarized in Table 2. The substrate **1a** with primary alcohol was selected as standard substrate and gave the unfamiliar product **2a** in 75% yield. The structure of the representative product **2a** was

determined by X-ray crystallographic analysis. Subsequently, manifold substituted secondary homopropargylic alcohol substrates were prepared to investigate the scope of this reaction. In the case of Ph-substituted substrate **1b**, the corresponding product **2b** was obtained in 57% yield. The reactions of substrates **1c**-**1i** bearing electron-donating or electron-withdrawing substituents resulted in the corresponding products **2c**-**2i** in moderate to good yields. The structure of **2h** was identified by X-ray crystallographic analysis. The substrate **1j** with 2-naphthyl group was also tolerated and the desired product **2j** was obtained in 63% yield. Afterward, substrate **1k** with piperonyl group was attempted and afforded the product **2k** in 55% yield. In contrast to the products containing aryl-substituents, the yields of **2l** and **2m** which had alkyl groups remarkably decreased because of the weak nucleophilicity of the hydroxyl group and the severe decomposition of the substrates. In particular, substrate **1n** with cinnamyl group only led to **2n** in 15% yield. However, substrate **1o** with a tertiary alcohol failed to afford the corresponding product **2o**. This might be due to the huge steric hindrance impairing the nucleophilicity of the hydroxyl group. The transformations also proceeded smoothly with substrates **1p**-**1s** with electron-donating or -withdrawing substituents on R^2, furnishing the products **2p**-**2s** in moderate to good yields. Fortunately, the substrate **1t** could work smoothly and gave the desired product **2t** in 61% yield. Subsequently, the ketone substrate **1u** was examined, however, the desired product **2u** was not observed. According to Barluenga's[19] and Larock's[20] work,

the ketone substrate provided 5-*exo*-*dig* rather than 6-*endo* intermediate, which was not compatible with this transformation. Thus, we failed to obtain the product **2u**. To further extend the application of this reaction, we designed the substrates **1v** and **1w**, achieved the desired products **2v** and **2w** in 48% and 81% yields, respectively. The structure of products **2v** and **2w** were also determined by X-ray crystallographic analysis.

Scheme 2. Scale-up Experiments

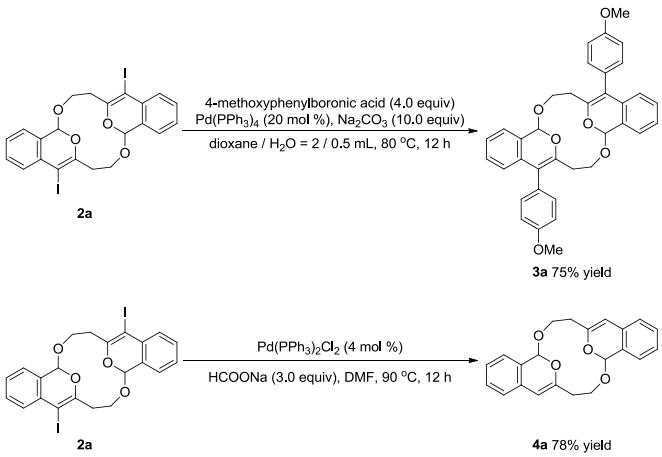


1a
5.75 mmol, 1 g

2a
57%, 0.98 g

It's worth noting that the reaction can be scaled up to gram quantities (Scheme 2). The desired product **2a** was isolated in 57% yield on the gram scale under the standard conditions, which provide possibilities for the industrial applications.

Scheme 3. Palladium-catalyzed Coupling and Reduction Reactions



2a

3a 75% yield

2a

4a 78% yield

As shown in Scheme 3, macrocyclic polyether **2a** can be further demonstrated by conducting relevant postfunctionalization reactions. For

example, the Suzuki coupling of **2a** afforded the corresponding product **3a** in 75% yield.[22] Furthermore, the product **4a** can be obtained in 78% yield by Pd-catalyzed reduction.[23]

CONCLUSION

In conclusion, a concise and mild protocol for the synthesis of diiodinated macrocyclic polyethers has been established. This new strategy relates to the incorporation of iodine and the diiodinated moiety is readily introduced into the macrocycles. Moreover, the resulting diiodinated macrocycle is readily elaborated to more products by palladium-catalyzed coupling and reduction reactions, which may be essential intermediates for the synthesis of other valuable compounds. The application of this methodology is currently underway.

EXPERIMENTAL SECTION

General Remarks

Column chromatography was carried out on silica gel. ^{1}H NMR spectra were recorded on 400 MHz in $CDCl_3$ and ^{13}C NMR spectra were recorded on 100 MHz in $CDCl_3$. IR spectra were recorded on a FT-IR spectrometer and only major peaks are reported in cm^{-1}. The substrates (**1a**-**1i** and **1u**-**1w**) are known compounds.[24] The substrates (**1j**-**1w**) and all products were further characterized by high resolution mass spectra (HRMS), the HRMS was obtained on a Q-Exactive Hybrid Quadrupole-Orbitrap Mass Sepctrometer. Copies of their ^{1}H NMR and ^{13}C NMR spectra are provided in the Supporting

Information. Room temperature is 23-25°C. The ICl was 0.5 M in CH_2Cl_2. THF was distilled over Na/benzophenone. DCE, CH_2Cl_2, CH_3CN, acetone and toluene were distilled over CaH_2, and other solvents were used without further purification.

General Procedure for Synthesis of Homopropargylic Alcohols

Method **A**: To a soluton of corresponding aldehydes (R^1-CHO, R^1 = aryl-, 2-naphthyl-, piperonyl-, cinnamyl-) (20 mmol) was dissolved in THF (8 mL) and added saturated aqueous NH_4Cl (40 mL). Subsequently, the propargyl bromide (2.0 equiv) was added into the mixture. Portions of activated zinc dust (2.0 equiv) were added slowly at 0 ^oC. The resulting solution was stirred for 1 h at 0 ^oC. Then, the reaction mixture was stirred at room temperature for 24 h. When the reaction was considered complete as determined by TLC analysis, the mixture was extracted by ethyl acetate (3 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4, the Na_2SO_4 was removed by decantation and the organic phase was concentrated under reduced pressure and purified by silica gel flash column chromatography (petroleum ether/EtOAc = 4/1) to provide corresponding homopropargylic alcohols in 60-85% yields.

Method **B**: A solution of Et_2O (30 mL), hexane (18 mL) and n-BuLi (2.4 mol/L in THF, 4.2 equiv) was cooled to -78 ^oC, the TMEDA (1.1 equiv) was added, followed by dropwise addition of propargyl bromide (2.0 equiv). The resulting solution was stirred for 20 min at -78 ^oC, then, a white precipitate formed. A solution of cyclopropanecarbaldehyde (10 mmol) in Et_2O (5 mL) was

added dropwise over 5 min and the reaction mixture were allowed to warm to room temperature over 2 h. When the reaction was considered complete as determined by TLC analysis, the mixture was quenched with water (30 mL) and extracted by ethyl acetate (3 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4, the Na_2SO_4 was removed by decantation and the organic phase was concentrated under reduced pressure and purified by silica gel flash column chromatography (petroleum ether/EtOAc = 4/1) to provide homopropargylic alcohol of 1-cyclopropylbut-3-yn-1-ol in 30% yield. The homopropargylic alcohol of 1,1-diphenylbut-3-yn-1-ol was synthesized from benzophenone according to the method **B**.

Other alcohols such as but-3-yn-1-ol, pent-4-yn-2-ol, pent-4-yn-1-ol and hex-5-yn-1-ol were obtained through purchase.

General Procedure for Synthesis 2-(4-hydroxybut-1-yn-1-yl)-benzaldehyde Derivatives (1a-1w)

To a soluton of 2-iodobenzaldehyde derivatives (7.5 mmol) in Et_3N (20 mL) was added $Pd(PPh_3)_2Cl_2$ (1 mol %) and CuI (2 mol %). The reaction vial was flushed with Ar and the reaction mixture was stirred for 5 minutes. A solution of corresponding homopropargylic alcohols (5 mmol) in Et_3N (5 mL) were then added dropwise through a syringe for 5 minutes. The resulting solution was stirred at room temperature overnight. When the reaction was considered complete as determined by TLC analysis, the mixture was quenched by addition of saturated aqueous NH_4Cl (20 mL) and extracted with ethyl acetate

(3 x 30 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4, the Na_2SO_4 was removed by decantation and the organic phase was concentrated under reduced pressure. The crude material was purified by flash column chromatography (petroleum ether/EtOAc = 4/1) to give the substrates **1** (**1a**-**1u**) in 70-85% yields. The substrate **1v** was synthesized from pent-4-yn-1-ol according to general procedure as mentioned above. The substrate **1w** was synthesized from hex-5-yn-1-ol according to general procedure as mentioned above. The reaction to the synthesis of substrate **1w** was run at 60 ^{o}C.

General Procedure for Synthesis of Diiodinated Diepoxydibenzo[*c*,*k*][1,9]dioxacyclohexadecines

To a solution of 2-(4-hydroxybut-1-yn-1-yl)benzaldehyde derivatives **1** (0.20 mmol) and NaOAc (2.0 equiv) in DCE (4.0 mL) was added ICl (1.2 equiv) dropwise at room temperature. When the reaction was considered complete as determined by TLC analysis, the reaction mixture was quenched by addition of saturated aqueous sodium thiosulfate (10 mL) and diluted with ethyl acetate (3 x 10 mL), washed with water, saturated brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by chromatography on silica gel (petroleum ether/CH_2Cl_2 = 2/1) to afford **2**.

Typical Procedure for 3a: To a solution of **2a** (120.0 mg, 0.20 mmol) in dioxane/H_2O (2/0.5 mL) was added 4-methoxyphenylboronic acid (121.6 mg, 4.0 equiv), $Pd(PPh_3)_4$ (46.2 mg, 20 mol %) and Na_2CO_3 (212 mg, 10.0 equiv).

The reaction vial was flushed with Ar and the reaction mixture was stirred at 80 °C for 12 h. Afterwards, the reaction mixture was quenched with H_2O (10 mL) and extracted with ethyl ether (3 x 10 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4, the Na_2SO_4 was removed by decantation and the organic phase was concentrated under reduced pressure. The crude material was purified by flash column chromatography (petroleum ether/EtOAc = 10/1) to give **3a** (yield 75%) as a yellow solid.

Typical Procedure for 4a: To a solution of **2a** (120.0 mg, 0.20 mmol) in DMF (2 mL) was added $Pd(PPh_3)_2Cl_2$ (5.6 mg, 4 mol %) and HCOONa (41 mg, 3.0 equiv). The reaction vial was flushed with Ar and the reaction mixture was stirred at 90 °C for 12 h. The reaction mixture was quenched with H_2O (10 mL) and extracted with ethyl ether (3 x 10 mL). The combined organic layers were washed with water, brine, dried over Na_2SO_4, the Na_2SO_4 was removed by decantation and the organic phase was concentrated under reduced pressure. The crude material was purified by flash column chromatography (petroleum ether/EtOAc = 10/1) to give **4a** (yield 78%) as a white solid.

Characterization Data of 1a−1w

*2-(4-hydroxybut-1-yn-1-yl)benzaldehyde (**1a**)*. Yellow oil (0.72 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.44 (s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.54-7.51 (m, 2H), 7.42-7.38 (m, 1H), 3.87 (q, J = 6.0 Hz, 2H), 2.98 (s, 1H), 2.76 (t, J = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 192.1, 135.8, 133.7, 133.3, 128.1, 126.5, 94.4, 78.2, 60.8, 23.8.

*2-(4-hydroxy-4-phenylbut-1-yn-1-yl)benzaldehyde (**1b**)*. Pale yellow solid (1.0 g, 80%). mp: 56-58 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.24 (s, 1H), 7.83 (d, J = 7.6 Hz, 1H), 7.52-7.42 (m, 4H), 7.41-7.35 (m, 3H), 7.33-7.29 (m, 1H), 4.99 (t, J = 6.0 Hz, 1H), 3.07 (s, 1H), 2.94 (d, J = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 192.0, 142.6, 136.0, 133.6, 133.3, 128.5, 128.2, 128.1, 128.0, 126.3, 125.7, 93.7, 79.0, 72.4, 30.5.

*2-(4-hydroxy-4-(o-tolyl)but-1-yn-1-yl)benzaldehyde (**1c**)*. Pale yellow oil (1.06 g, 80%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.26 (s, 1H), 7.82 (d, J = 7.6 Hz, 1H), 7.56 (d, J = 6.8 Hz, 1H), 7.51-7.45 (m, 2H), 7.39-7.35 (m, 1H), 7.26-7.17 (m, 2H), 7.14 (d, J = 7.2 Hz, 1H), 5.24-5.20 (m, 1H), 3.12 (s, 1H), 2.90-2.88 (m, 2H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 192.0, 140.6, 135.9, 134.4, 133.6, 133.3, 130.3, 128.1, 128.1, 127.7, 126.4, 126.2, 125.1, 93.9, 78.7, 68.8, 29.2, 19.0.

*2-(4-hydroxy-4-(m-tolyl)but-1-yn-1-yl)benzaldehyde (**1d**)*. Pale yellow oil (1.08 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.23 (s, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.50-7.44 (m, 2H), 7.36 (t, J = 7.2 Hz, 1H), 7.27-7.19 (m, 3H), 7.11 (d, J = 6.8 Hz, 1H), 4.93 (t, J = 6.0 Hz, 1H), 3.17 (s, 1H), 2.92-2.90 (m, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 192.0, 142.5, 138.0, 135.9, 133.6, 133.3, 128.7, 128.3, 128.1, 127.9, 126.5, 126.4, 122.7, 93.8, 78.8, 72.4, 30.4, 21.3.

*2-(4-hydroxy-4-(p-tolyl)but-1-yn-1-yl)benzaldehyde (**1e**)*. Pale yellow oil (1.03 g, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.24 (s, 1H), 7.82 (d, J = 7.6 Hz, 1H),

7.51-7.45 (m, 2H), 7.39-7.35 (m, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 4.95 (t, *J* = 6.0 Hz, 1H), 3.01 (s, 1H), 2.93-2.91 (m, 2H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* ppm 192.0, 139.6, 137.7, 136.0, 133.6, 133.3, 129.1, 128.1, 127.9, 126.5, 125.7, 93.9, 78.8, 72.3, 30.4, 21.1.

*2-(4-hydroxy-4-(4-methoxyphenyl)but-1-yn-1-yl)benzaldehyde (**1f**)*. Pale yellow oil (1.18 g, 84%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 10.24 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.51-7.45 (m, 2H), 7.39 (d, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 4.96-4.92 (m, 1H), 3.79 (s, 3H), 3.06 (s, 1H), 2.97-2.86 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* ppm 192.0, 159.2, 136.0, 134.8, 133.6, 133.3, 128.1, 127.9, 127.0, 126.5, 113.8, 93.9, 78.8, 72.1, 55.2, 30.4.

*2-(4-(4-chlorophenyl)-4-hydroxybut-1-yn-1-yl)benzaldehyde (**1g**)*. Pale yellow oil (1.21 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 10.26 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.53-7.49 (m, 1H), 7.45 (d, *J* = 6.8 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.37-7.31 (m, 4H), 4.97 (t, *J* = 6.4 Hz, 1H), 3.40 (s, 1H), 2.90 (d, *J* = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* ppm 192.0, 141.1, 135.9, 133.7, 133.5, 133.4, 128.6, 128.5, 128.3, 127.1, 125.9, 93.2, 79.4, 71.7, 30.6.

*2-(4-(4-bromophenyl)-4-hydroxybut-1-yn-1-yl)benzaldehyde (**1h**)*. Yellow oil (1.37 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 10.27 (s, 1H), 7.83-7.81 (m, 1H), 7.53-7.45 (m, 4H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 4.96 (t, *J* = 6.0 Hz, 1H), 3.37 (s, 1H), 2.90 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* ppm 191.9, 141.6, 135.9, 133.7, 133.4, 131.5, 128.7, 128.3, 127.5,

125.9, 121.7, 93.2, 79.5, 71.7, 30.5.

2-(4-hydroxy-4-(4-(trifluoromethyl)phenyl)but-1-yn-1-yl)benzaldehyde ***(1i)***. Pale yellow solid (1.14 g, 72%). mp: 76-78 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.26 (s, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.51-7.49 (m, 1H), 7.45 (d, *J* = 6.4 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 5.06 (t, *J* = 6.0 Hz, 1H), 3.65 (s, 1H), 2.99-2.88 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 192.0, 146.6, 135.9, 133.7, 133.4, 130.0 (q, $^{1}J_{C\text{-}F}$ = 32 Hz), 129.0, 128.3, 126.1, 125.7, 125.3 (q, $^{2}J_{C\text{-}F}$ = 4 Hz), 122.7, 92.9, 79.7, 71.7, 30.6.

2-(4-hydroxy-4-(naphthalen-2-yl)but-1-yn-1-yl)benzaldehyde ***(1j)***. Pale yellow oil (1.19 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.27 (s, 1H), 7.85 (s, 1H), 7.82-7.76 (m, 4H), 7.52-7.49 (m, 1H), 7.46-7.40 (m, 4H), 7.35-7.30 (m, 1H), 5.13-5.10 (m, 1H), 3.35 (s, 1H), 2.98 (d, *J* = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 191.9, 140.0, 135.9, 133.6, 133.3, 133.1, 133.0, 128.2, 128.2, 128.1, 127.9, 127.6, 126.2, 126.2, 126.0, 124.6, 123.6, 93.7, 79.1, 72.5, 30.5. HRMS (ESI) m/z Calcd for $C_{21}H_{16}O_2Na$: $[M+Na]^+$ = 323.1043. Found: 323.1045.

2-(4-(benzo[d][1,3]dioxol-5-yl)-4-hydroxybut-1-yn-1-yl)benzaldehyde ***(1k)***. Yellow oil (1.10 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.24 (s, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.52-7.45 (m, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 6.93 (s, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 5.94 (s, 1H), 4.89 (t, *J* = 6.0 Hz, 1H), 3.16 (s, 1H), 2.94-2.83 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm

192.0, 147.7, 147.2, 136.6, 135.9, 133.6, 133.3, 128.1, 128.0, 126.4, 119.2, 108.0, 106.2, 101.0, 93.7, 78.9, 72.3, 30.5. HRMS (ESI) m/z Calcd for $C_{18}H_{14}O_4Na$: $[M+Na]^+$ = 317.0784. Found: 317.0782.

*2-(4-hydroxypent-1-yn-1-yl)benzaldehyde (**1l**)*. Yellow oil (0.76 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.45 (s, 1H), 7.55-7.52 (m, 2H), 7.43-7.39 (m, 1H), 4.16-4.08 (m, 1H), 2.87 (s, 1H), 2.73-2.61 (m, 2H), 1.36 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 191.9, 135.9, 133.7, 133.4, 128.2, 128.1, 126.5, 94.0, 78.8, 66.3, 30.0, 22.5. HRMS (ESI) m/z Calcd for $C_{12}H_{13}O_2$: $[M+H]^+$ = 189.0910. Found: 189.0909.

*2-(4-cyclopropyl-4-hydroxybut-1-yn-1-yl)benzaldehyde (**1m**)*. Yellow oil (0.75 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.48 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 4.4 Hz, 2H), 7.43-7.39 (m, 1H), 3.24-3.19 (m, 1H), 2.88-2.76 (m, 2H), 2.55 (s, 1H), 1.14-1.06 (m, 1H), 0.61-0.57 (m, 2H), 0.45-0.40 (m, 1H), 0.35-0.31 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 192.0, 136.0, 133.6, 133.3, 128.1, 127.9, 126.7, 94.3, 78.5, 74.7, 28.3, 17.0, 2.9, 2.6. HRMS (ESI) m/z Calcd for $C_{14}H_{14}O_2Na$: $[M+Na]^+$ = 237.0886. Found: 237.0887.

*2-(4-hydroxy-6-phenylhex-5-en-1-yn-1-yl)benzaldehyde (**1n**)*. Brown oil (1.04 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.43 (s, 1H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.50-7.47 (m, 2H), 7.39-7.35 (m, 3H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.25-7.21 (m, 1H), 6.70 (d, *J* = 16.0 Hz, 1H), 6.33 (dd, *J* = 16, 6.4 Hz, 1H), 4.59 (q, *J* = 6.0 Hz, 1H), 3.06 (s, 1H), 2.88-2.78 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 191.9, 136.2, 135.9, 133.6, 133.4, 131.2, 130.2, 128.5, 128.2, 128.1, 127.8, 126.5,

126.3, 93.4, 79.0, 70.9, 28.8. HRMS (ESI) m/z Calcd for $C_{19}H_{16}O_2Na$: $[M+Na]^+$ = 299.1043. Found: 299.1040.

*2-(4-hydroxy-4,4-diphenylbut-1-yn-1-yl)benzaldehyde (**1o**)*. Pale yellow solid (1.17 g, 72%). mp: 110-112 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.92 (s, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 4H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.38-7.32 (m, 6H), 7.26 (t, *J* = 7.2 Hz, 2H), 3.48 (s, 1H), 3.45 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 191.7, 145.4, 136.1, 133.5, 133.4, 128.4, 128.2, 127.3, 126.0, 125.8, 93.3, 80.3, 77.7, 34.7. HRMS (ESI) m/z Calcd for $C_{23}H_{18}O_2Na$: $[M+Na]^+$ = 349.1199. Found: 349.1197.

*2-(4-hydroxybut-1-yn-1-yl)-4-methylbenzaldehyde (**1p**)*. Pale yellow solid (0.73 g, 78%). mp: 22-24 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.37 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.33 (s, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 3.87 (t, *J* = 6.4 Hz, 2H), 2.75 (t, *J* = 6.4 Hz, 2H), 2.56 (s, 1H), 2.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 191.6, 144.8, 133.9, 133.8, 129.2, 128.6, 126.3, 93.7, 78.6, 61.0, 24.0, 21.6. HRMS (ESI) m/z Calcd for $C_{12}H_{13}O_2$: $[M+H]^+$ = 189.0910. Found: 189.0908.

*2-(4-hydroxybut-1-yn-1-yl)-5-methylbenzaldehyde (**1q**)*. Yellow solid (0.76 g, 81%). mp: 44-46 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.40 (s, 1H), 7.65 (s, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 3.86 (t, *J* = 6.4 Hz, 2H), 2.87 (s, 1H), 2.75 (t, *J* = 6.4 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 192.2, 138.4, 135.7, 134.6, 133.2, 128.4, 123.7, 93.3, 78.2, 60.9, 23.9, 21.1. HRMS (ESI) m/z Calcd for $C_{12}H_{13}O_2$: $[M+H]^+$ = 189.0910. Found:

189.0910.

*4-chloro-2-(4-hydroxybut-1-yn-1-yl)benzaldehyde (**1r**)*. Pale yellow oil (0.89 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.38 (s, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.49 (s, 1H), 7.37 (d, J = 8.4 Hz, 1H), 3.88 (t, J = 6.4 Hz, 2H), 2.84 (s, 1H), 2.76 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 190.8, 140.1, 134.2, 133.1, 129.3, 129.6, 128.0, 95.9, 77.0, 60.7, 23.8. HRMS (ESI) m/z Calcd for $C_{11}H_{10}ClO_2$: $[M+H]^+$ = 209.0364. Found: 209.0363.

*5-chloro-2-(4-hydroxybut-1-yn-1-yl)benzaldehyde (**1s**)*. Pale yellow oil (0.82 g, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.39 (s, 1H), 7.81 (s, 1H), 7.50-7.44 (m, 2H), 3.87 (t, J = 6.4 Hz, 2H), 2.76 (t, J = 6.4 Hz, 2H), 2.65 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 190.7, 137.0, 134.6, 133.7, 127.7, 124.9, 95.5, 77.2, 60.8, 23.9. HRMS (ESI) m/z Calcd for $C_{11}H_{10}ClO_2$: $[M+H]^+$ = 209.0364. Found: 209.0363.

*3-(4-hydroxybut-1-yn-1-yl)-2-naphthaldehyde (**1t**)*. Yellow solid (0.82 g, 73%). mp: 64-66 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.45 (s, 1H), 8.26 (s, 1H), 7.91 (s, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.55 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.2 Hz, 1H), 3.92 (t, J = 6.4 Hz, 2H), 3.30 (s, 1H), 2.79 (t, J = 6.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 192.1, 135.2, 133.3, 132.3, 131.6, 131.4, 129.6, 129.3, 127.4, 127.3, 120.3, 93.1, 78.9, 60.9, 24.0. HRMS (ESI) m/z Calcd for $C_{15}H_{13}O_2$: $[M+H]^+$ = 225.0910. Found: 225.0909.

*1-(2-(4-hydroxybut-1-yn-1-yl)phenyl)ethanone (**1u**)*. Pale yellow oil (0.77 g, 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75-7.73 (m, 1H), 7.52-7.50 (m, 1H),

7.45-7.41 (m, 1H), 7.38-7.34 (m, 1H), 3.85 (t, *J* = 6.0 Hz, 2H), 3.23 (s, 1H), 2.70 (t, *J* = 6.0 Hz, 2H), 2.66 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* ppm 199.9, 139.8, 134.0, 131.5, 129.1, 127.7, 122.0, 92.8, 81.9, 60.9, 29.2, 24.2. HRMS (ESI) m/z Calcd for $C_{12}H_{13}O_2$: $[M+H]^+$ = 189.0910. Found: 189.0909.

*2-(5-hydroxypent-1-yn-1-yl)benzaldehyde (**1v**)*. Pale yellow oil (0.71 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 10.50 (s, 1H), 7.86 (d, *J* = 7.6 Hz, 1H), 7.53-7.48 (m, 2H), 7.40-7.36 (m, 1H), 3.82 (t, *J* = 6.4 Hz, 2H), 2.62 (t, *J* = 7.2 Hz, 2H), 2.58 (s, 1H), 1.93-1.87 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* ppm 192.2, 135.8, 133.7, 133.2, 127.9, 127.4, 127.1, 97.1, 76.6, 61.2, 31.1, 16.0. HRMS (ESI) m/z Calcd for $C_{12}H_{13}O_2$: $[M+H]^+$ = 189.0910. Found: 189.0909.

*2-(6-hydroxyhex-1-yn-1-yl)benzaldehyde (**1w**)*. Pale yellow oil (0.71 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 10.52 (s, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.54-7.49 (m, 2H), 7.40-7.36 (m, 1H), 3.72 (t, *J* = 6.0 Hz, 2H), 2.54 (t, *J* = 6.8 Hz, 2H), 2.10 (s, 1H), 1.79-1.72 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* ppm 192.2, 135.8, 133.7, 133.3, 127.9, 127.6, 127.0, 97.6, 76.0, 62.1, 31.8, 24.8, 19.3. HRMS (ESI) m/z Calcd for $C_{13}H_{15}O_2$: $[M+H]^+$ = 203.1067. Found: 203.1065.

Characterization Data of Products

*(9E,19E)-10,20-diiodo-5,9,15,19-diepoxy-5,7,8,15,17,18-hexahydrodibenzo[c, k][1,9]dioxacyclohexadecine (**2a**)*. White solid (45.0 mg, 75%). mp: 154-156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* ppm 7.39 (d, *J* = 8.0 Hz, 2H), 7.36-7.32 (m, 2H), 7.25-7.21 (m, 2H), 7.11 (d, *J* = 7.2 Hz, 2H), 5.93 (s, 2H), 4.55-4.49 (m, 2H),

3.83-3.79 (m, 2H), 3.48-3.40 (m, 2H), 2.51-2.46 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.7, 131.2, 129.4, 128.8, 127.4, 126.9, 125.2, 97.2, 75.8, 64.7, 37.1. IR (neat, cm^{-1}): 2865, 1614, 1483, 1118, 1098, 1004, 969, 758. HRMS (ESI) m/z Calcd for $C_{22}H_{19}I_2O_4$: $[M+H]^+$ = 600.9367. Found: 600.9367.

*(9E,19E)-10,20-diiodo-5,9,15,19-diepoxy-7,17-diphenyl-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2b**)*. White solid (42.9 mg, 57%). mp: 190-192 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.62 (d, *J* = 7.2 Hz, 4H), 7.52 (t, *J* = 7.2 Hz, 4H), 7.44-7.40 (m, 4H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.24-7.20 (m, 2H), 6.89 (d, *J* = 7.2 Hz, 2H), 5.85 (s, 2H), 5.55 (dd, *J* = 11.2, 2.4 Hz, 2H), 3.54-3.47 (m, 2H), 2.59 (dd, *J* = 14.4, 2.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.0, 141.1, 131.4, 129.2, 128.9, 128.8, 128.4, 127.4, 127.3, 126.9, 124.7, 94.1, 76.2, 75.8, 46.0. IR (neat, cm^{-1}): 2922, 1613, 1454, 1168, 1075, 988, 757, 697. HRMS (ESI) m/z Calcd for $C_{34}H_{27}I_2O_4$: $[M+H]^+$ = 752.9993. Found: 752.9990.

*(9E,19E)-10,20-diiodo-5,9,15,19-diepoxy-7,17-di-o-tolyl-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2c**)*. White solid (49.9 mg, 64%). mp: 246-248 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.68 (s, 2H), 7.44-7.34 (m, 6H), 7.32-7.21 (m, 6H), 6.95 (d, *J* = 7.2 Hz, 2H), 5.89-5.87 (m, 2H), 5.81 (s, 2H), 3.42-3.26 (m, 2H), 2.59 (s, 6H), 2.53 (dd, *J* = 14.8, 2.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.0, 139.2, 135.6, 131.4, 130.6, 129.3, 128.8, 128.0, 127.4, 126.9, 126.0, 124.7, 93.9, 76.1, 71.3, 44.7, 19.1. IR (neat, cm^{-1}): 2920, 1616, 1485, 1079, 1038, 991, 757, 578. HRMS (ESI) m/z Calcd for

$C_{36}H_{31}I_2O_4$: $[M+H]^+$ = 781.0306. Found: 781.0307.

*(9E,19E)-10,20-diiodo-5,9,15,19-diepoxy-7,17-di-m-tolyl-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2d**)*. White solid (49.1 mg, 63%). mp: 222-224 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.43-7.40 (m, 8H), 7.37-7.33 (m, 2H), 7.24-7.20 (m, 4H), 6.89 (d, *J* = 6.8 Hz, 2H), 5.85 (s, 2H), 5.52 (dd, *J* = 11.2, 2.4 Hz, 2H), 3.52-3.46 (m, 2H), 2.59 (dd, *J* = 14.4, 2.4 Hz, 2H), 2.48 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.1, 141.1, 138.6, 131.4, 129.2, 129.1, 128.8, 128.8, 128.0, 127.4, 126.8, 124.7, 124.2, 94.0, 76.1, 75.9, 45.9, 21.6. IR (neat, cm^{-1}): 2919, 1613, 1484, 1080, 1040, 992, 756, 705. HRMS (ESI) m/z Calcd for $C_{36}H_{31}I_2O_4$: $[M+H]^+$ = 781.0306. Found: 781.0303.

*(9E,19E)-10,20-diiodo-5,9,15,19-diepoxy-7,17-di-p-tolyl-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2e**)*. White solid (46.8 mg, 60%). mp: 232-234 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.51 (d, *J* = 8.0 Hz, 4H), 7.41 (d, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 4H), 7.21 (t, *J* = 7.2 Hz, 2H), 6.88 (d, *J* = 7.6 Hz, 2H), 5.84 (s, 2H), 5.51 (dd, *J* = 11.6, 2.4 Hz, 2H), 3.52-3.45 (m, 2H), 2.57 (dd, *J* = 14.4, 2.4 Hz, 2H), 2.44 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.1, 138.2, 138.1, 131.4, 129.6, 129.2, 128.7, 127.4, 127.3, 126.8, 124.7, 94.0, 76.1, 75.7, 46.0, 21.3. IR (neat, cm^{-1}): 2918, 1610, 1482, 1082, 1039, 991, 814, 753. HRMS (ESI) m/z Calcd for $C_{36}H_{31}I_2O_4$: $[M+H]^+$ = 781.0306. Found: 781.0301.

(9E,19E)-10,20-diiodo-5,9,15,19-diepoxy-7,17-bis(4-methoxyphenyl)-5,7,8,15,

*17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2f**)*. White solid (47.1 mg, 58%). mp: 204-206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.54 (d, *J* = 8.4 Hz, 4H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 4H), 6.86 (d, *J* = 7.2 Hz, 2H), 5.83 (s, 2H), 5.49 (dd, *J* = 11.2, 2.4 Hz, 2H), 3.89 (s, 6H), 3.52-3.46 (m, 2H), 2.57 (dd, *J* = 14.4, 2.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 159.7, 150.2, 133.0, 131.4, 129.2, 128.7, 128.6, 127.5, 126.8, 124.7, 114.3, 93.9, 76.1, 75.4, 55.4, 46.0. IR (neat, cm^{-1}): 2925, 1614, 1249, 1175, 1034, 985, 830, 761. HRMS (ESI) m/z Calcd for $C_{36}H_{31}I_2O_6$: $[M+H]^+$ = 813.0205. Found: 813.0198.

*(9E,19E)-10,20-diiodo-5,9,15,19-diepoxy-7,17-bis(4-chlorophenyl)-10,20-diiodo-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2g**)*. White solid (54.1 mg, 66%). mp: 212-214 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.55 (d, *J* = 8.4 Hz, 4H), 7.48 (d, *J* = 8.4 Hz, 4H), 7.42 (d, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.23 (t, *J* = 6.8 Hz, 2H), 6.86 (d, *J* = 7.2 Hz, 2H), 5.79 (s, 2H), 5.49 (dd, *J* = 11.6, 2.4 Hz, 2H), 3.49-3.42 (m, 2H), 2.55 (dd, *J* = 14.4, 2.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 149.2, 139.6, 134.2, 131.2, 129.4, 129.2, 128.9, 128.6, 127.0, 124.7, 94.1, 76.4, 75.1, 45.8. IR (neat, cm^{-1}): 2917, 1614, 1482, 1080, 1037, 994, 823, 755. HRMS (ESI) m/z Calcd for $C_{34}H_{25}Cl_2I_2O_4$: $[M+H]^+$ = 820.9214. Found: 820.9208.

*(9E,19E)-10,20-diiodo-5,9,15,19-diepoxy-7,17-bis(4-bromophenyl)-10,20-diiodo-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2h**)*. White solid (58.1 mg, 64%). mp: 236-238 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.64

(d, *J* = 8.0 Hz, 4H), 7.49 (d, *J* = 8.4 Hz, 4H), 7.42 (d, *J* = 6.8 Hz, 2H), 7.38-7.34 (m, 2H), 7.25-7.21 (m, 2H), 6.86 (d, *J* = 6.8 Hz, 2H), 5.80 (s, 2H), 5.48 (dd, *J* = 11.6, 2.4 Hz, 2H), 3.48-3.42 (m, 2H), 2.55 (dd, *J* = 14.4, 2.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 149.4, 140.1, 132.1, 131.2, 129.4, 129.0, 128.9, 127.0, 127.0, 124.7, 122.4, 94.1, 76.4, 75.1, 45.8. IR (neat, cm^{-1}): 2918, 1615, 1480, 1078, 1037, 993, 819, 754. HRMS (ESI) m/z Calcd for $C_{34}H_{25}Br_2I_2O_4$: $[M+H]^+$ = 908.8203. Found: 908.8208.

*(9E,19E)-10,20-diiodo-5,9,15,19-diepoxy-7,17-bis(4-(trifluoromethyl)phenyl)-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2i**)*. White solid (49.7 mg, 56%). mp: 214-216 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.79 (d, *J* = 8.4 Hz, 4H), 7.75 (d, *J* = 8.4 Hz, 4H), 7.44 (d, *J* = 7.2 Hz, 2H), 7.38 (t, *J* = 7.2 Hz, 2H), 7.28-7.24 (m, 2H), 6.90 (d, *J* = 7.2 Hz, 2H), 5.82 (s, 2H), 5.60 (dd, *J* = 11.6, 2.4 Hz, 2H), 3.51-3.45 (m, 2H), 2.59 (dd, *J* = 14.4, 2.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 149.1, 145.3, 131.2, 130.8 (q, $^1J_{C\text{-}F}$ = 33 Hz), 129.6, 129.0, 127.5, 127.2, 126.9, 126.0 (d, $^2J_{C\text{-}F}$ = 3 Hz), 125.4, 124.7, 94.3, 76.6, 75.2, 45.9. IR (neat, cm^{-1}): 2924, 1617, 1326, 1125, 1167, 994, 840, 759. HRMS (ESI) m/z Calcd for $C_{36}H_{25}F_6I_2O_4$: $[M+H]^+$ = 888.9741. Found: 888.9741.

*(9E,19E)-10,20-diiodo-5,9,15,19-diepoxy-7,17-di(naphthalen-2-yl)-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2j**)*. White solid (53.7 mg, 63%). mp: 232-234 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.12 (s, 2H), 8.04 (d, *J* = 8.8 Hz, 2H), 7.99 (d, *J* = 7.6 Hz, 2H), 7.95 (d, *J* = 7.2 Hz, 2H),

7.79-7.76 (m, 2H), 7.62-7.55 (m, 4H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.39-7.35 (m, 2H), 7.25-7.21 (m, 2H), 6.88 (d, *J* = 7.2 Hz, 2H), 5.91 (s, 2H), 5.78 (dd, *J* = 11.6, 2.8 Hz, 2H), 3.68-3.61 (m, 2H), 2.69 (dd, *J* = 14.8, 2.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.0, 138.4, 133.5, 133.4, 131.5, 129.3, 129.1, 128.9, 128.0, 127.9, 127.4, 126.9, 126.9, 126.6, 126.4, 124.8, 124.6, 94.2, 76.3, 76.1, 45.8. IR (neat, cm^{-1}): 2919, 1608, 1482, 1080, 1037, 989, 819, 753. HRMS (ESI) m/z Calcd for $C_{42}H_{31}I_2O_4$: $[M+H]^+$ = 853.0306. Found: 853.0300.

(9E,19E)-7,17-bis(benzo[d][1,3]dioxol-5-yl)-10,20-diiodo-5,9,15,19-diepoxy-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (***2k***). White solid (45.9 mg, 55%). mp: 218-220 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.41 (d, *J* = 7.2 Hz, 2H), 7.37-7.33 (m, 2H), 7.24-7.20 (m, 2H), 7.10-7.07 (m, 4H), 6.91 (t, *J* = 8.0 Hz, 4H), 6.06-6.03 (m, 4H), 5.85 (s, 2H), 5.42 (dd, *J* = 11.6, 2.4 Hz, 2H), 3.49-3.42 (m, 2H), 2.55 (dd, *J* = 14.4, 2.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 149.9, 148.4, 147.7, 135.0, 131.4, 129.2, 128.8, 127.3, 126.9, 124.7, 121.0, 108.4, 107.2, 101.3, 93.9, 76.2, 75.6, 46.0. IR (neat, cm^{-1}): 2921, 1613, 1484, 1247, 1039, 987, 797, 757. HRMS (ESI) m/z Calcd for $C_{36}H_{27}I_2O_8$: $[M+H]^+$ = 840.9790. Found: 840.9788.

(9E,19E)-10,20-diiodo-5,9,15,19-diepoxy-7,17-dimethyl-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (***2l***). White solid (22.6 mg, 36%). mp: 158-160 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.41 (d, *J* = 7.6 Hz, 2H), 7.36-7.32 (m, 2H), 7.25-7.21 (m, 2H), 7.07 (d, *J* = 7.6 Hz, 2H), 6.11 (s, 2H), 4.65-4.58 (m, 2H), 3.21-3.14 (m, 2H), 2.39 (dd, *J* = 14.4, 2.0 Hz, 2H), 1.41 (d, *J*

= 6.0 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.3, 131.6, 129.2, 128.6, 127.3, 126.7, 124.7, 93.1, 75.7, 68.0, 44.6, 18.6. IR (neat, cm^{-1}): 2925, 1615, 1374, 1176, 1128, 1067, 1001, 758. HRMS (ESI) m/z Calcd for $C_{24}H_{23}I_2O_4$: $[M+H]^+$ = 628.9680. Found: 628.9675.

*(9E,19E)-7,17-dicyclopropyl-10,20-diiodo-5,9,15,19-diepoxy-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2m**)*. White solid (21.7 mg, 32%). mp: 176-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.40 (d, *J* = 7.2 Hz, 2H), 7.36-7.32 (m, 2H), 7.25-7.21 (m, 2H), 7.13 (d, *J* = 6.8 Hz, 2H), 6.56 (s, 2H), 3.65-3.60 (m, 2H), 3.31-3.25 (m, 2H), 2.53 (dd, *J* = 14.4, 2.4 Hz, 2H), 1.04-2.99 (m, 2H), 0.96-0.92 (m, 2H), 0.77-0.70 (m, 2H), 0.61-0.54 (m, 2H), 0.23-0.17 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.4, 131.6, 129.1, 128.6, 127.6, 126.6, 124.8, 92.8, 77.3, 75.8, 43.0, 14.1, 6.6, -0.4. IR (neat, cm^{-1}): 2915, 1616, 1382, 1087, 1061, 1036, 992, 758. HRMS (ESI) m/z Calcd for $C_{28}H_{27}I_2O_4$: $[M+H]^+$ = 680.9993. Found: 680.9994.

*(9E,19E)-10,20-diiodo-5,9,15,19-diepoxy-7,17-distyryl-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2n**)*. White solid (12.6 mg, 15%). mp: 146-148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.55 (d, *J* = 7.2 Hz, 4H), 7.44-7.40 (m, 6H), 7.38-7.34 (m, 4H), 7.24-7.22 (m, 2H), 7.05 (d, *J* = 6.8 Hz, 2H), 6.96 (d, *J* = 16 Hz, 2H), 6.29 (dd, *J* = 16, 8.4 Hz, 2H), 6.14 (s, 2H), 5.13-5.08 (m, 2H), 3.44-3.38 (m, 2H), 2.59 (dd, *J* = 14.4, 2.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 149.6, 136.0, 134.7, 131.5, 129.3, 128.8, 128.8, 128.3, 128.0, 127.3, 126.9, 126.7, 124.9, 93.6, 76.2, 74.4, 43.4. IR (neat, cm^{-1}):

2923, 1612, 1454, 1078, 1036, 989, 752, 695. HRMS (ESI) m/z Calcd for $C_{38}H_{31}I_2O_4$: $[M+H]^+$ = 805.0306. Found: 805.0305.

*(9E,19E)-10,20-diiodo-5,9,15,19-diepoxy-2,12-dimethyl-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2p**)*. White solid (37.0 mg, 59%). mp: 194-196 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.19 (s, 2H), 7.05-7.00 (m, 4H), 5.91 (s, 2H), 4.55-4.49 (m, 2H), 3.81-3.78 (m, 2H), 3.47-3.40 (m, 2H), 2.50-2.45 (m, 2H), 2.37 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.7, 139.2, 130.9, 129.3, 127.6, 125.2, 124.9, 97.2, 75.9, 64.7, 37.1, 21.6. IR (neat, cm^{-1}): 2892, 1615, 1450, 1098, 1040, 1010, 977, 812. HRMS (ESI) m/z Calcd for $C_{24}H_{23}I_2O_4$: $[M+H]^+$ = 628.9680. Found: 628.9686.

*(9E,19E)-10,20-diiodo-5,9,15,19-diepoxy-3,13-dimethyl-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2q**)*. White solid (28.3 mg, 45%). mp: 168-170 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.28-7.25 (m, 2H), 7.16-7.13 (m, 2H), 6.94 (s, 2H), 5.89 (s, 2H), 4.55-4.49 (m, 2H), 3.82-3.78 (m, 2H), 3.46-3.38 (m, 2H), 2.50-2.45 (m, 2H), 2.36 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 149.8, 136.7, 130.1, 128.7, 127.3, 125.7, 97.3, 75.8, 64.7, 37.0, 21.0. IR (neat, cm^{-1}): 2863, 1616, 1495, 1103, 1036, 1010, 969, 820. HRMS (ESI) m/z Calcd for $C_{24}H_{23}I_2O_4$: $[M+H]^+$ = 628.9680. Found: 628.9680.

*(9E,19E)-2,12-dichloro-10,20-diiodo-5,9,15,19-diepoxy-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2r**)*. White solid (38.1 mg, 57%). mp: 206-208 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.42 (d, J = 1.6 Hz, 2H), 7.21-7.19 (m, 2H), 7.06 (d, J = 7.6 Hz, 2H), 5.91 (s, 2H), 4.51-4.45 (m, 2H),

3.83-3.79 (m, 2H), 3.46-3.38 (m, 2H), 2.52-2.47 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 151.9, 135.4, 133.0, 128.9, 126.9, 126.7, 125.6, 96.7, 74.0, 64.7, 37.1. IR (neat, cm^{-1}): 2918, 1609, 1474, 1100, 1033, 1009, 969, 814. HRMS (ESI) m/z Calcd for $C_{22}H_{17}Cl_2I_2O_4$: $[M+H]^+$ = 668.8588. Found: 668.8599.

*(9E,19E)-3,13-dichloro-10,20-diiodo-5,9,15,19-diepoxy-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**2s**)*. White solid (36.1 mg, 54%). mp: 218-220 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.34 (d, J = 8.4 Hz, 2H), 7.31-7.28 (m, 2H), 7.13-7.12 (m, 2H), 5.88 (s, 2H), 4.51-4.45 (m, 2H), 3.83-3.79 (m, 2H), 3.46-3.38 (m, 2H), 2.51-2.46 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 151.0, 132.2, 130.4, 129.8, 129.4, 128.3, 125.1, 96.5, 74.5, 64.8, 36.9. IR (neat, cm^{-1}): 2903, 1618, 1480, 1096, 1038, 1010, 967, 805. HRMS (ESI) m/z Calcd for $C_{22}H_{17}Cl_2I_2O_4$: $[M+H]^+$ = 668.8588. Found: 668.8594.

*(10E,22E)-11,23-diiodo-6,10,18,22-diepoxy-6,8,9,18,20,21-hexahydrodinaphtho[2,3-c:2',3'-k][1,9]dioxacyclohexadecine (**2t**)*. White solid (42.7 mg, 61%). mp: 204-206 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.85 (t, J = 8.4 Hz, 4H), 7.80 (s, 2H), 7.63 (s, 2H), 7.49-7.41 (m, 4H), 6.10 (s, 2H), 4.62-4.56 (m, 2H), 3.93-3.90 (m, 2H), 3.54-3.46 (m, 2H), 2.56-2.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 151.2, 134.0, 132.3, 129.1, 128.2, 127.6, 127.4, 127.3, 126.6, 125.7, 124.5, 97.4, 76.6, 64.9, 37.4. IR (neat, cm^{-1}): 2895, 1614, 1318, 1101, 1004, 966, 877, 746. HRMS (ESI) m/z Calcd for $C_{30}H_{23}I_2O_4$: $[M+H]^+$ = 700.9680. Found: 700.9685.

(10E,21E)-11,22-diiodo-5,10,16,21-diepoxy-5,7,8,9,16,18,19,20-octahydrodib

*enzo[c,l][1,10]dioxacyclooctadecine (**2v**)*. White solid (30.1 mg, 48%). mp: 124-126 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.44 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.26 (d, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 7.6 Hz, 2H), 6.01 (s, 2H), 4.02 (q, *J* = 8.4 Hz, 2H), 3.75-3.69 (m, 2H), 3.01-2.93 (m, 2H), 2.63-2.57 (m, 2H), 2.09-2.02 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 153.1, 130.7, 129.7, 128.5, 127.2, 126.8, 125.8, 98.8, 74.6, 66.6, 32.7, 27.3. IR (neat, cm^{-1}): 2904, 1603, 1480, 1061, 1090, 997, 970, 754. HRMS (ESI) m/z Calcd for $C_{24}H_{23}I_2O_4$: $[M+H]^+$ = 628.9680. Found: 628.9685.

*(11E,23E)-12,24-diiodo-5,11,17,23-diepoxy-5,7,8,9,10,17,19,20,21,22-decahydrodibenzo[c,m][1,11]dioxacycloicosine (**2w**)*. White solid (53.1 mg, 81%). mp: 178-180 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.41 (d, *J* = 7.6 Hz, 2H), 7.37-7.33 (m, 2H), 7.25-7.21 (m, 2H), 7.09 (d, *J* = 7.6 Hz, 2H), 5.92 (s, 2H), 3.93-3.87 (m, 2H), 3.71-3.65 (m, 2H), 3.14-3.07 (m, 2H), 2.57-2.52 (m, 2H), 1.80-1.66 (m, 6H), 1.61-1.53 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 153.3, 130.7, 129.6, 129.1, 127.1, 127.1, 125.4, 98.0, 75.1, 68.8, 36.1, 27.5, 24.6. IR (neat, cm^{-1}): 2856, 1609, 1455, 1074, 1019, 987, 937, 760. HRMS (ESI) m/z Calcd for $C_{26}H_{27}I_2O_4$: $[M+H]^+$ = 656.9993. Found: 656.9999.

*(9E,19E)-10,20-bis(4-methoxyphenyl)-5,9,15,19-diepoxy-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**3a**)*. Yellow solid (84.0 mg, 75%). mp: 100-102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.29-7.16 (m, 8H), 7.12-7.00 (m, 2H), 6.78-6.74 (m, 4H), 6.69-6.56 (m, 2H), 5.95 (s, 2H), 4.51-4.46 (m, 2H), 3.66 (s, 6H), 3.63-3.59 (m, 2H), 2.56-2.49 (m, 2H),

2.20-2.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 158.3, 147.1, 132.1, 128.8, 128.0, 126.9, 125.6, 125.3, 122.8, 115.7, 113.0, 103.1, 96.5, 63.1, 54.9, 31.9. IR (neat, cm^{-1}): 2903, 1644, 1511, 1242, 1098, 1006, 970, 754. HRMS (ESI) m/z Calcd for $C_{36}H_{33}O_6$: $[M+H]^+$ = 561.2272. Found: 561.2276.

*(9E,19E)-5,9,15,19-diepoxy-5,7,8,15,17,18-hexahydrodibenzo[c,k][1,9]dioxacyclohexadecine (**4a**)*. White solid (54.3 mg, 78%). mp: 242-244 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.27-7.23 (m, 2H), 7.18-7.17 (m, 4H), 6.96 (d, J = 7.6 Hz, 2H), 6.00 (s, 2H), 5.76 (s, 2H), 4.64-4.58 (m, 2H), 3.75-3.73 (m, 2H), 2.59-2.45 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 150.3, 130.4, 129.1, 126.6, 125.9, 125.7, 123.5, 103.0, 97.6, 63.5, 34.5. IR (neat, cm^{-1}): 2921, 1657, 1399, 1093, 1048, 996,962, 756. HRMS (ESI) m/z Calcd for $C_{22}H_{21}O_4$: $[M+H]^+$ = 349.1434. Found: 349.1439.

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Crystallographic file of **2a** (CIF)

Crystallographic file of **2h** (CIF)

Crystallographic file of **2v** (CIF)

Crystallographic file of **2w** (CIF)

Copies of ^{1}H NMR, ^{13}C NMR spectra. (PDF)

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Notes

The authors declare no competing financial interest.

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