Expedited Articles

Orally Active, Water-Soluble Antimalarial 3-Aryltrioxanes: Short Synthesis and Preclinical Efficacy Testing in Rodents

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Short chemical syntheses of four new antimalarial trioxanes are presented, starting with inexpensive and commercially available cyclohexanone. Almost exclusive formation of the trioxane 12α-stereoisomers simplifies product purification. Carboxyphenyltrioxanes **3** and **5** are thermally stable in air even at 60 °C for 24 h. When administered orally, these new carboxyphenyltrioxanes are highly efficacious in curing malaria-infected mice. Important for their practical in vivo administration, these new synthetic antimalarial trioxanes **3** and **5** are 14−20 times more soluble in water at pH 7.4 than is artelinic acid (**1**), a leading semisynthetic, herb-derived antimalarial trioxane drug candidate.

Introduction

About 40% of the world's population is currently at risk for contracting the infectious parasitic disease malaria.[1] On the basis of ancient Chinese folk herbal medicine,[2−4] several derivatives of the natural 1,2,4-trioxane artemisinin are now used as fast-acting chemotherapeutic drugs to cure individuals who have malaria.[5−7] One such artemisinin derivative is water-soluble trioxane artelinic acid (**1**), designed by the U.S.
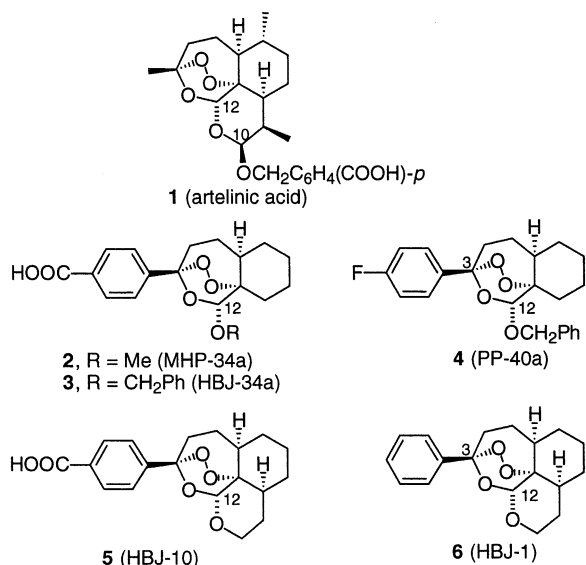

Walter Reed Army Institute of Research, and it is a leading candidate for antimalarial drug development.[8,9]

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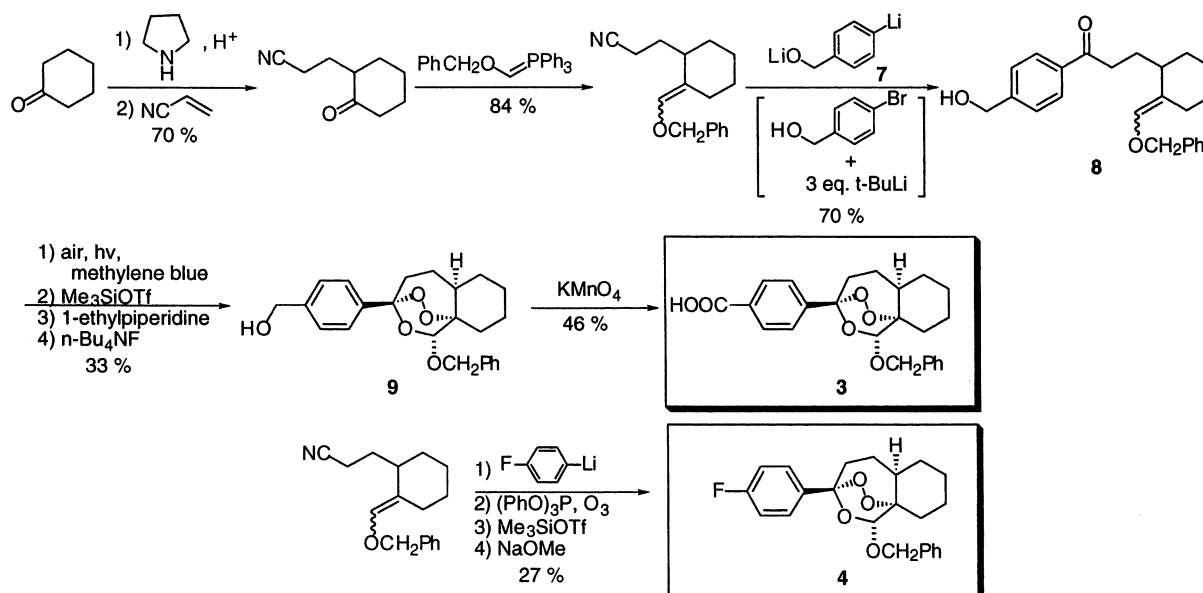† School of Arts and Sciences.
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Starting from cyclohexanone, we recently developed a five-step total synthesis of water-soluble simplified 3-carboxyphenyltrioxane **2** that has at least as good a therapeutic index (efficacy/toxicity) as that of nature-derived artelinic acid (**1**) in rodents.[10] Now we report on second-generation water-soluble synthetic carboxyphenyltrioxanes **3** and **5**, in which the design of trioxane **5** was inspired by the pioneering work of Oh and colleagues.[11] Noteworthy characteristics of these new chemical entities **3** and **5**, as described in detail below, include especially their high solubility in water and their high chemotherapeutic efficacy upon oral administration to malaria-infected mice.

Chemistry

Short syntheses of simplified trioxanes **3** and **5**, as well as of their corresponding 3-fluorophenyl analogue **4** and 3-phenyl analogue **6**, are shown in Schemes 1 and 2. Noteworthy features of these synthetic routes are as follows: (1) in Scheme 1, use of 4-bromobenzyl alcohol in the form of its dianion **7** to produce benzylic alcohol ketone **8** directly (i.e., without alcohol protection−deprotection) in 70% yield; (2) air photooxygenation without protecting the benzylic hydroxyl group; (3) almost exclusive formation of the 12α-benzyloxy product **9** (with only a trace of the easily separable 12β-benzyloxy diastereomer); (4) in Scheme 2, intramolecular formation and effective use of cyclic vinyl ether **10** to form keto vinyl ether **11**; (5) successful photooxygenation of keto ether **11** into styryltrioxane **12** with exclusive formation of only the 12α-pyran stereoisomer.

The 12α-stereochemistry of new trioxanes **3**−**6** was established by a combination of their NMR spectroscopic characteristics[12] and chromatographic polarities. As we have seen previously in similar trioxanes,[10] the 12α-stereoisomers are more polar than the corresponding 12β-isomers upon TLC and HPLC chromatography.

Scheme 1

Scheme 2

Like MHP-34a (**2**), 12α-benzyloxytrioxanes **3** and **4** have characteristic ^{1}H NMR peaks at δ 2.3 and at δ 2.5, respectively, and also characteristic ^{13}C NMR peaks for the C_{12}-acetal carbon atom at δ 94 and δ 98, respectively (in contrast to δ 104−105 for the 12β-diastereomers; see Experimental Section). Likewise, the α-pyrans **5** and **6** have characteristic C_{12}−H ^{1}H NMR singlets at δ 5.5 and δ 5.4, respectively.

The thermal stability of new synthetic trioxanes **3** and **5** is very good. Heating crystalline trioxanes **3** and **5** in air at 60 °C for 24 h caused less than 5% decomposition, as judged by ^{1}H NMR spectroscopy. Also, heating a pH 7.4 phosphate-buffered 0.1 N NaCl solution of trioxane **3** at 40 °C for 7 days caused less than 5% decomposition, as judged by ^{1}H NMR spectroscopy. Under these pH 7.4 buffered conditions, trioxane **5** showed approximately 20% decomposition.

Biology

Because in vitro antimalarial testing generally indicates only very low activity for water-soluble trioxanes, we evaluated carboxyphenyltrioxanes **3** and **5** directly via in vivo testing in mice following an established protocol.[13] Efficacy against *P. berghei* malaria parasites was studied using oral administration as the most challenging mode of drug delivery. Results are summarized in Table 1. Whereas first-generation carboxyphenyltrioxane **2** is about 5 times less efficacious than artelinic acid (**1**),[10] carboxyphenyltrioxanes **3** and **5** both are about only 2 times less efficacious than artelinic acid. Importantly, however, these two new trioxanes are considerably more soluble in pH 7.4 buffered water than is **1**; trioxane **3** is about 14 times more soluble (7 mg/mL) than **1**, and trioxane **5** is about 20 times more soluble (10 mg/mL). This relatively high water solubility

Table 1. Antimalarial Efficacy in Mice Against *P. berghei*

compd	ED$_{50}$,[a] mg/kg	ED$_{90}$,[a] mg/kg
1	9.6	29.0
3	17.0	59.0
5	15.0	51.0

[a] Four different doses were administered each day for 4 days to five mice per dose regimen to establish the ED values indicated here using a previously described protocol.[13]

of new trioxanes **3** and **5** means that they can be administered in vivo orally or intravenously in considerably more concentrated aqueous solutions than can **1**. No overt signs of toxicity were observed in these in vivo antimalarial experiments.

For comparison with hydrophilic trioxane **3**, the corresponding but hydrophobic 3-*p*-fluorophenyltrioxane **4** was prepared (Scheme 1) and was evaluated for in vitro antimalarial activity following an established protocol.[14] Relative to artemisinin with an IC$_{50}$ of 9.4 nM, water-insoluble fluorophenyltrioxane **4** has an IC$_{50}$ of 31 nM. Also, for comparison with hydrophilic trioxane **5**, hydrophobic 3-phenyltrioxane **6** was prepared; it has an in vitro antimalarial IC$_{50}$ of 1.3 nM. Although hydrophobic 3-fluorophenyl **4** and especially 3-phenyltrioxanes **6** have high in vitro antimalarial activities, they could not be easily administered in vivo intravenously or orally because of their insolubility in water.

In conclusion, new structurally simple, synthetic 3-carboxyphenyltrioxanes **3** and **5** are highly water-soluble and orally efficacious antimalarial compounds that deserve further preclinical evaluation as potential drugs for malaria chemotherapy.[15–18]

Experimental Section[19]

Preparation of 2-(2′-Cyanoethyl)-1-(benzyloxymethylene)cyclohexane. A solution of (benzyloxymethyl)triphenylphosphonium chloride[20] (2.19 g, 5.23 mmol) in THF (40 mL) was put in a methanol bath fixed at −43 °C. To this solution was added *n*-BuLi (1.6 M in hexanes, 3.3 mL, 5.28 mmol) slowly by syringe. The solution turned red and was stirred for 30 min. To the resultant ylide solution was added a solution of 2-cyanoethylcyclohexanone[21] (0.40 g, 2.65 mmol) in THF (4 mL) via cannula, and then it was stirred for 20 h at −43 °C. The reaction mixture was quenched with water and extracted with ether. The organic layer was separated, dried over MgSO$_4$, and concentrated. The residue was subjected to column chromatography with EtOAc/hexanes (1:10) as eluent to give the product (0.57 g, 84%, *Z/E* = 1/3) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.25−7.36 (m, 5H), 5.98 (s), and 5.89 (s) (1H total), 4.68−4.77 (m, 2H), 2.93 (m), and 2.49 (dt, J_d=14.0 Hz, J_t=4.0 Hz) (1H total), 1.98−2.20 (m, 3H), 1.76−1.92 (m, 2H), 1.43−1.72 (m, 6H), 1.13−1.32 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 139.4, 138.5, 137.5, 137.3, 128.24, 128.21, 127.7, 127.6, 127.4, 127.3, 120.4, 119.8, 118.7, 117.8, 105.9, 73.4, 73.3, 37.4, 32.5, 31.1, 27.8, 27.4, 26.8, 26.7, 26.2, 22.2, 21.9, 21.5, 15.0. HRMS (M + Na) calcd 278.1515, found 278.1511.

Preparation of *p*-Fluorophenyltrioxane 4. To a solution of *p*-bromofluorobenzene (0.49 g, 2.80 mmol) in ether (30 mL) at −78 °C was added *t*-BuLi (1.6 M in pentane, 2.9 mL, 4.64 mmol) via syringe over 1 min. The resulting solution was stirred at −78 °C for 30 min. A precooled (−78 °C) solution of 2-(2′-cyanoethyl)-1-(benzyloxymethylene)cyclohexane (0.48 g, 1.68 mmol) in ether (20 mL) was then added dropwise via cannula for 2 min. The resulting mixture was stirred at −78 °C for 30 min, then the cooling bath was removed, and the reaction mixture was allowed to reach room temperature. At this point, TLC analysis indicated full consumption of the starting material. The reaction was quenched with 5 mL of

saturated aqueous NaHCO$_3$, and the mixture was poured into a separatory funnel containing 50 mL of ether and 30 mL of water. The organic layer was further washed with 20 mL of saturated aqueous NaCl, dried over MgSO$_4$, and concentrated. The residue was subjected to column chromatography with EtOAc/hexanes (1:10) as eluent to give the *p*-fluorophenyl ketone intermediate (0.60 g, 92%) as a pale-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.87−7.91 (m, 2H), 7.26−7.34 (m, 5H), 7.04−7.12 (m, 2H), 5.97 (d, *J* = 2.0 Hz), and 5.84 (s) (1H total), 4.59−4.76 (m, 2H), 2.77−3.01 (m), and 2.40 (dt, J_d=14.0 Hz, J_t=4.4 Hz) (3H total), 1.95−2.06 (m, 3H), 1.78−1.85 (m, 1H), 1.49−1.76 (m, 5H), 1.14−1.40 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 199.3, 199.0, 165.5 (d, $J_{C−F}$ = 252 Hz), 165.4 (d, $J_{C−F}$ = 252 Hz), 138.8, 137.99, 137.96, 137.88, 133.6 (d, $J_{C−F}$ = 3.1 Hz), 133.5 (d, $J_{C−F}$ = 3.1 Hz), 130.58 (d, $J_{C−F}$ = 9.1 Hz), 130.56 (d, $J_{C−F}$ = 9.1 Hz), 128.35, 128.34, 127.7, 127.6, 127.3, 127.2, 121.0, 119.9, 115.5 (d, $J_{C−F}$ = 21.9 Hz), 115.4 (d, $J_{C−F}$ = 21.9 Hz), 73.4, 73.3, 38.6, 36.9, 36.7, 33.6, 32.8, 31.8, 28.3, 27.2, 26.5, 25.9, 25.8, 22.9, 22.8, 21.6. HRMS (EI, M$^+$) calcd 352.1839, found 352.1844.

A flame-dried 250 mL three-necked round-bottom flask was charged with triphenyl phosphite (1.02 g, 3.29 mmol) in dry CH$_2$Cl$_2$ (55 mL) at room temperature. The mixture was cooled to −78 °C, and ozone generated from UHP oxygen was bubbled through the solution until saturation was indicated by a deep-blue color of the solution. The mixture was then purged with Ar until the mixture was colorless. To this mixture was slowly added a precooled (−78 °C) solution of the *p*-fluorophenyl ketone intermediate (*Z/E* = 1/1, 0.58 g, 1.65 mmol) in dry CH$_2$Cl$_2$ (30 mL) via cannula. The reaction mixture was stirred at −78 °C and monitored continuously by TLC. TLC after 30 min showed no starting material. To this mixture at −78 °C was added dropwise a precooled (−78 °C) solution of Me$_3$SiOTf (TMSOTf, 0.33 mL, 1.82 mmol) in CH$_2$Cl$_2$ (5 mL) via cannula for 2 min. The resulting mixture was stirred at −78 °C until all dioxetane intermediate was consumed as indicated by TLC. At that time, the reaction mixture was treated with a 25 wt % solution of sodium methoxide in MeOH (3.3 equiv), and the reaction mixture was warmed to room temperature. The mixture was diluted with H$_2$O and CHCl$_3$. The organic layer was separated, washed with brine, dried over MgSO$_4$, and concentrated. The residue was subjected to column chromatography with EtOAc/hexanes (1:10) as eluent to give 12α-benzyloxytrioxane **4** (0.18 g, 29%) and 12β-benzyloxytrioxane (0.17 g, 27%). Further purification of 12α-benzyloxytrioxane **4** by HPLC (silica, 3% EtOAc/hexanes, 3.0 mL/min, 254 nm, R_t = 14.5 min) afforded a white solid: mp 116−117 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.54 (m, 2H), 7.30−7.52 (m, 5H), 7.04 (m, 2H), 5.28 (s, 1H), 5.00 (d, *J* = 12.6 Hz, 1H), 4.78 (d, *J* = 12.6 Hz, 1H), 2.83 (ddd, J_d = 14.4, 13.2, 4.0 Hz, 1H), 2.47 (m, 1H), 2.26 (ddd, J_d = 14.4, 4.8, 2.8 Hz, 1H), 1.69−1.84 (m, 3H), 1.54−1.64 (m, 3H), 1.06−1.26 (m, 3H), 0.93 (qt, J_q = 13.6 Hz, J_t = 3.2 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 162.9 (d, $J_{C−F}$ = 247 Hz), 137.4, 136.5 (d, $J_{C−F}$ = 3.2 Hz), 128.39, 128.36, 127.9, 127.5 (d, $J_{C−F}$ = 8.6 Hz), 115.1 (d, $J_{C−F}$ = 21.8 Hz), 103.8, 98.4, 83.7, 69.5, 45.5, 37.6, 33.4, 32.5, 27.1, 25.1, 22.7. HRMS (CI, M + H$^+$) calcd 385.1815, found 385.1820. Further purification of 12β-benzyloxytrioxane by HPLC (silica, 3% EtOAc/hexanes, 3.0 mL/min, 254 nm, R_t = 9.0 min) afforded a white solid: mp 59−60 °C. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.50 (m, 2H), 7.30−7.43 (m, 5H), 7.04 (m, 2H), 5.34 (d, *J* = 1.2 Hz, 1H), 5.10 (d, *J* = 12.0 Hz, 1H), 4.74 (d, *J* = 12.0 Hz, 1H), 2.79 (ddd, J_d = 14.6, 13.4, 3.6 Hz, 1H), 2.31 (ddd, J_d = 14.6, 4.2, 3.2 Hz, 1H), 2.05 (m, 1H), 1.72−1.88 (m, 4H), 1.60−1.72 (m, 4H), 1.29 (m, 1H), 1.19 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 162.9 (d, $J_{C−F}$ = 247 Hz), 137.3, 136.7 (d, $J_{C−F}$ = 3.7 Hz), 128.4, 127.9, 127.8, 127.3 (d, $J_{C−F}$ = 8.2 Hz), 115.1 (d, $J_{C−F}$ = 21.4 Hz), 104.8, 102.7, 83.9, 71.2, 47.5, 39.1, 35.5, 30.9, 26.8, 25.0, 24.0.

Preparation of *p*-(Hydroxymethyl)phenyl Ketone 8. To a solution of *p*-bromobenzyl alcohol (0.22 g, 1.18 mmol) in ether (20 mL) at −78 °C was added *t*-BuLi (1.4 M in pentane, 2.5 mL, 3.60 mmol, 3 equiv) via syringe over 1 min. The resulting solution was stirred at −78 °C for 30 min. A precooled (−78 °C) solution of 2-(2′-cyanoethyl)-1-(benzyloxymethylene)cyclo-

hexane (0.20 g, 0.78 mmol) in ether (10 mL) was then added dropwise via cannula for 2 min. The resulting mixture was warmed to room temperature slowly and stirred overnight. The reaction was quenched with 3 mL of saturated aqueous NaHCO$_3$, and the mixture was poured into a separatory funnel containing 50 mL of ether and 20 mL of water. The aqueous layer was further extracted with 30 mL of ether. The organic layer was collected, dried over MgSO$_4$, and concentrated. The residue was subjected to column chromatography with EtOAc/hexanes (1:2) as eluent to give the ketone **8** (0.20 g, 70%) as a pale-yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.86 (m, 2H), 7.26−7.42 (m, 7H), 5.97 (d, $J = 1.2$ Hz), and 5.86 (s) (1H total), 4.61−4.74 (m, 2H), 2.77−3.01 (m), and 2.40 (dt, J_d=13.6 Hz, J_t=4.8 Hz) (3H total), 2.51 (br s, 1H), 1.91−2.08 (m, 3H), 1.49−1.85 (m, 6H), 1.18−1.40 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 200.8, 200.5, 146.0, 145.8, 138.7, 137.90, 137.86, 136.3, 136.1, 128.3, 128.2, 127.6, 127.2, 126.5, 126.4, 121.0, 120.0, 73.3, 73.2, 64.5, 64.4, 38.6, 37.0, 36.8, 33.5, 32.8, 31.7, 28.2, 27.1, 26.4, 26.0, 25.8, 22.9, 22.7, 21.5. HRMS (M + Na) calcd 387.1931, found 387.1934.

Preparation of *p*-(Hydroxymethyl)phenyltrioxane 9. A 100 mL three-necked round-bottom flask equipped with dispersion bubbler gas inlet, gas outlet, and a septum was charged with *p*-(hydroxymethyl)phenyl ketone **8** (*Z*/*E* = 1/3, 104 mg, 0.29 mmol) in dry CH$_2$Cl$_2$ (30 mL), and about 1 mg of methylene blue was added. To the solution maintained at −78 °C was bubbled dry air at a flow rate of ∼240 mL/min. Irradiation was achieved via a 250 W IR lamp (General Electric) at 1 in distance from the reaction flask. TLC analysis after 20 min showed no starting material, at which time the IR lamp was removed. The air bubbler and outlet also were removed, and the reaction mixture was placed under an Ar atmosphere. A precooled (−78 °C) solution of Me$_3$SiOTf (0.13 mL, 0.72 mmol, 2.5 equiv) in CH$_2$Cl$_2$ (3 mL) was added slowly via cannula for 2 min. The reaction was stirred for 1 h at −78 °C, then quenched with 1-ethylpiperidine (0.16 mL, 4 equiv) by syringe. The reaction mixture was allowed to warm to room temperature and then concentrated. To the residue was added dry THF (10 mL), and 1.5 mL of 1 M TBAF (tetra-*n*-butylammonium fluoride) in THF was added to the solution at 0 °C. The resulting solution was stirred for 1 h at room temperature. The reaction mixture was quenched with 3 mL of water and poured into a separatory funnel containing 20 mL of EtOAc and 10 mL of water. The aqueous layer was further extracted with 20 mL of EtOAc. The organic layer was collected, washed with saturated NaCl solution, dried over MgSO$_4$, and concentrated. The residue was subjected to column chromatography with EtOAc/hexanes (1:3) as eluent to give the α-benzyltrioxane **9** (38 mg, 33%) as a colorless oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.56 (m, 2H), 7.30−7.42 (m, 7H), 5.29 (s, 1H), 5.00 (d, $J = 12.0$ Hz, 1H), 4.77 (d, $J = 12.0$ Hz, 1H), 4.71 (s, 2H), 2.84 (ddd, J_d=14.8, 12.8, 4.0 Hz, 1H), 2.48 (dm, $J_d = 13.2$ Hz, 1H), 2.28 (dm, $J_d = 14.8$ Hz, 1H), 1.69−1.84 (m, 4H), 1.55−1.64 (m, 3H), 1.07−1.26 (m, 3H), 0.94 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 141.4, 140.0, 137.4, 128.4, 127.8, 126.7, 125.7, 104.0, 93.2, 83.7, 69.3, 64.9, 45.5, 37.6, 33.4, 32.5, 27.1, 25.1, 22.7. HRMS (M + Na) calcd 419.1829, found 419.1843.

Preparation of *p*-Carboxyphenyltrioxane 3. A solution of *p*-benzyltrioxane **9** (25 mg, 0.063 mmol) and KMnO$_4$ (30 mg) in acetone (5 mL) was stirred for 4 h (no starting material by TLC) at room temperature, generating a precipitate. The precipitate was filtered and washed with more acetone, and then it was dissolved in H$_2$O (5 mL). The filtrate was acidified with aqueous 0.5 N HCl solution to pH 2, generating a white solid, which was filtered and recrystallized from MeOH/H$_2$O at room temperature to give 12 mg (46%) of **3** as a white solid: mp 192.5−193.5 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.96 (d, $J = 7.2$ Hz, 2H), 7.64 (d, $J = 8.0$ Hz, 2H), 7.30−7.37 (m, 5H), 5.52 (s, 1H), 4.96 (d, $J = 12.0$ Hz, 1H), 4.75 (d, $J = 12.0$ Hz, 1H), 2.75 (t, $J = 13.6$ Hz, 1H), 2.28 (d, $J = 11.6$ Hz, 1H), 2.18 (d, $J = 13.6$ Hz, 1H), 1.49−1.79 (m, 6H), 1.06−1.28 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.8, 144.5, 137.9, 131.1, 129.4, 128.3, 127.9, 127.7, 125.7, 103.1, 93.8, 83.4, 69.5,

45.1, 37.2, 33.2, 31.6, 26.7, 24.8, 22.2. HRMS (M + Na) calcd 433.1622, found 433.1600. Anal. Calcd for C$_{24}$H$_{26}$O$_6$: C, 70.23; H, 6.38. Found: C, 69.94; H, 6.22.

For the 12β-stereoisomer. ^{1}H NMR (400 MHz, CD$_3$OD): δ 8.01−8.04 (m, 2H), 7.59−7.62 (m, 2H), 7.31−7.47 (m, 5H), 5.34 (s, 1H), 5.08 (d, $J = 12.0$ Hz, 1H), 4.78 (d, $J = 12.0$ Hz, 1H), 2.80 (ddd, J_d=14.4, 12.0, 3.6 Hz, 1H), 2.25 (ddd, J_d=14.8, 4.4, 3.2 Hz, 1H), 2.06 (m, 1H), 1.65−1.89 (m, 8H), 1.22−1.30 (m, 2H). ^{13}C NMR (100 MHz, CD$_3$OD): δ 169.5, 147.0, 139.0, 132.4, 130.9, 129.6, 129.5, 129.1, 126.6, 106.3, 104.3, 85.2, 72.7, 49.1, 40.4, 36.7, 32.2, 28.1, 26.3, 25.2.

Preparation of Cyclic Enol Ether 10. A solution of 0.90 g (4.03 mmol) of 2-(2′-cyanoethyl)-6-(2′-hydroxyethyl)-1-(methoxymethylene)cyclohexane[19] and 60 mg of *p*-TsOH in toluene (60 mL) was heated to reflux under Dean−Stark conditions for 4 h. The reaction mixture was cooled to room temperature, a few of drops of triethylamine were added to the solution, and then it was concentrated. The residue was subjected to column chromatography quickly with CH$_2$Cl$_2$ as eluent to give 0.63 g (83%) of **10** as a yellow oil. ^{1}H NMR (400 MHz, CDCl$_3$): δ 6.08 (s, 1H), 3.74−3.88 (m, 2H), 2.33−2.48 (m, 2H), 1.88−2.03 (m, 4H), 1.75−1.83 (m, 3H), 1.35−1.59 (m, 3H), 1.09 (m, 1H), 0.90 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 136.1, 119.8, 119.1, 63.8, 38.6, 34.8, 33.3, 33.0, 30.5, 27.1, 25.6, 15.0. HRMS (M + Na) calcd 214.1202, found 214.1194.

Preparation of 3-Phenyltrioxane 6. A solution of 0.45 g (2.4 mmol) of **10** in Et$_2$O (40 mL) was cooled to −78 °C. In a separate flask, 12 mL of PhLi (1.0 M in ether/cyclohexane) was precooled to −78 °C and cannulated to the solution. The resulting solution was stirred at −78 °C for 1 h, then at room temperature for 1 h. The reaction mixture was cooled to 0 °C and slowly quenched with saturated NaHCO$_3$. The aqueous layer was extracted with Et$_2$O, and the organic layer was separated, dried over MgSO$_4$, and concentrated. The residue was subjected to column chromatography with CH$_2$Cl$_2$ as eluent to give 0.46 g (71%) of phenyl ketone intermediate as a pale-yellow solid: mp 72.5−73.5 °C. ^{1}H NMR (CDCl$_3$): δ 7.98−7.95 (m, 2H), 7.56−7.46 (m, 3H), 6.22 (s, 1H), 3.91−3.76 (m, 2H), 3.13−2.98 (m, 2H), 2.04−1.63 (m, 8H), 1.56−1.35 (m, 2H), 1.26−0.94 (m, 2H). ^{13}C NMR (CDCl$_3$): δ 200.37, 136.96, 136.27, 132.91, 128.53, 128.00, 120.11, 63.77, 39.61, 36.40, 35.15, 34.22, 33.20, 30.64, 25.98, 25.63.

A 100 mL three-necked round-bottom flask equipped with dispersion bubbler gas inlet, gas outlet, and a septum was charged with the phenyl ketone intermediate (0.12 g, 0.44 mmol) in dry CH$_2$Cl$_2$ (25 mL), and about 1 mg of methylene blue was added. To the solution at −78 °C was bubbled dry air at a flow rate of ∼240 mL/min. Irradiation was achieved via a 250 W IR lamp at 1 in. distance from the reaction flask. The reaction was monitored continuously by TLC. TLC after 1 h showed no starting material, and then the IR lamp was removed. The air bubbler and outlet were removed, and the reaction was placed under an Ar atmosphere. A precooled (−78 °C) solution of TBSOTf (0.15 mL, 0.66 mmol) in CH$_2$Cl$_2$ (7 mL) was added slowly via cannula. The reaction mixture was stirred for 2 h at −78 °C, and then the reaction was quenched with NEt$_3$ (0.18 mL) by syringe. The reaction mixture was allowed to warm to room temperature and then concentrated. The residue was subjected to column chromatography with EtOAc/petroleum ether (1:9) as eluent to give the trioxane **6** (30 mg, 23%). Further purification of trioxane **6** by HPLC (silica, 10% EtOAc/hexanes, 2.0 mL/min, 254 nm, R_t = 19.3 min) afforded a white solid: mp 81−82 °C. ^{1}H NMR (CDCl$_3$): δ 7.60−7.58 (m, 2H), 7.36−7.30 (m, 3H), 5.44 (s, 1H), 3.97 (m, 1H), 3.81 (m, 1H), 2.88 (m, 1H), 2.47 (m, 1H), 2.32 (m, 1H), 1.87 (m, 1H), 1.80−1.59 (m, 7H), 1.42−1.25 (m, 2H), 1.15 (m, 1H). ^{13}C NMR (CDCl$_3$): δ 139.80, 128.90, 128.27, 125.68, 104.26, 92.22, 80.18, 61.36, 46.10, 39.85, 37.50, 32.60, 28.30, 26.95, 26.52, 25.01. HRMS calcd (M + Na) 325.1416, found 325.1414.

Preparation of *p*-Stylyl Ketone 11. To a solution of *p*-styryl bromide (0.22 g, 1.68 mmol) in ether (30 mL) at −78 °C was added *t*-BuLi (1.5 M in pentane, 2.2 mL, 3.20 mmol) via syringe over 1 min. The resulting dark-red solution was

stirred at −78 °C for 20 min. A precooled (−78 °C) solution of the nitrile **10** (0.22 g, 1.15 mmol) in ether (20 mL) was then added dropwise via cannula for 2 min. The resulting mixture was stirred at −78 °C for 30 min, then the cooling bath was removed, and the reaction mixture was allowed to reach room temperature. At this point, TLC analysis indicated full consumption of the starting material. The reaction was quenched with 5 mL of saturated aqueous NaHCO$_3$, and the mixture was poured into a separatory funnel containing 50 mL of ether and 30 mL of water. The organic layer was further washed with 20 mL of saturated aqueous NaCl, dried over MgSO$_4$, and concentrated. The residue was subjected to column chromatography with EtOAc/hexanes (1:12) as eluent to give the ketone **11** (0.245 g, 72%) as a sticky white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.91−7.94 (m, 2H), 7.46−7.49 (m, 2H), 6.75 (dd, J_d=17.6, 10.8 Hz, 1H), 6.22 (s, 1H), 5.87 (dd, J_d=17.6, 0.8 Hz, 1H), 5.39 (dd, J_d = 10.8, 0.8 Hz, 1H), 3.77−3.91 (m, 2H), 2.96−3.11 (m, 2H), 1.86−2.04 (m, 5H), 1.75−1.84 (m, 2H), 1.67 (m, 1H), 1.36−1.59 (m, 2H), 1.14 (m, 1H), 0.99 (m, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 199.7, 141.8, 136.2, 136.1, 135.9, 128.4, 126.2, 120.0, 116.5, 63.7, 39.6, 36.3, 35.1, 34.2, 33.2, 30.6, 25.9, 25.7.

Preparation of *p*-Stylyltrioxane 12. A 100 mL three-necked round-bottom flask equipped with dispersion bubbler gas inlet, gas outlet, and a septum was charged with the ketone **11** (0.22 g, 0.74 mmol) in dry CH$_2$Cl$_2$ (75 mL), and about 1.5 mg of methylene blue was added. To the solution at −78 °C was bubbled dry air at a flow rate of ~240 mL/min. Irradiation was achieved via a 250 W IR lamp at 1 in. distance from the reaction flask. The reaction was monitored continuously by TLC. TLC after 1 h showed no starting material, and then the IR lamp was removed. The air bubbler and outlet were removed, and the reaction mixture was placed under an Ar atmosphere. A precooled (−78 °C) solution of TMSOTf (0.27 mL, 1.48 mmol) in CH$_2$Cl$_2$ (7 mL) was added slowly via cannula. The reaction mixture was stirred for 2 h at −78 °C, and then the reaction was quenched with 1-ethylpiperidine (0.31 mL) by syringe. The reaction mixture was allowed to warm to room temperature and then concentrated. The residue was subjected to column chromatography with EtOAc/hexanes (1:10) as eluent to give the trioxane **12** (79 mg, 33%) as a sticky white solid. ^{1}H NMR (400 MHz, CDCl$_3$): δ 7.54 (d, J = 8.4 Hz, 2H), 7.37 (d, J = 8.4 Hz, 2H), 6.68 (dd, J_d = 17.6, 10.8 Hz, 1H), 5.74 (d, J = 17.6 Hz, 1H), 5.43 (s, 1H), 5.24 (d, J = 10.8 Hz, 1H), 3.97 (dd, J_d = 11.6, 4.0 Hz, 1H), 3.81 (m, 1H), 2.87 (m, 1H), 2.46 (tt, J_t = 13.2, 4.8 Hz, 1H), 2.31 (dm, J_d = 14.4 Hz, 1H), 1.86 (dt, J_d = 13.2 Hz, J_t = 2.4 Hz, 1H), 1.58−1.82 (m, 7H), 1.23−1.43 (m, 2H), 1.15 (d, J = 13.2 Hz, 1H). ^{13}C NMR (100 MHz, CDCl$_3$): δ 139.2, 138.1, 136.3, 126.1, 126.0, 114.5, 104.2, 92.2, 80.2, 61.4, 46.1, 39.4, 37.5, 32.6, 28.3, 26.9, 26.5, 25.0. HRMS (M + Na) calcd 351.1567, found 351.1571.

Preparation of *p*-Carboxyphenyltrioxane 5. A solution of *p*-styryltrioxane **12** (61 mg, 0.19 mmol) and KMnO$_4$ (118 mg) in acetone (6 mL) was stirred for 2 h (no starting material by TLC) at room temperature, generating a precipitate. The precipitate was filtered and washed with more acetone, and then it was dissolved in MeOH (20 mL). The filtrate was rotary-evaporated, and the residue was dissolved in water (4 mL). The aqueous solution was acidified with aqueous 0.5 N HCl solution to pH 2, generating a white solid, which was filtered and recrystallized from MeOH/*i*-PrOH at room temperature to give 33 mg (50%) of **5**: mp 153−154 °C (white solid). ^{1}H NMR (400 MHz, CD$_3$OD): δ 7.93 (dm, J_d = 8.4 Hz, 2H), 7.56 (dm, J_d = 8.4 Hz, 2H), 5.51 (s, 1H), 3.80−3.96 (m, 2H), 2.86 (m, 1H), 2.27−2.40 (m, 2H), 1.59−1.91 (m, 8H), 1.32−1.47 (m, 2H), 1.19 (d, J = 14.0 Hz, 1H). ^{13}C NMR (100 MHz, CD$_3$OD): δ 175.0, 143.3, 140.0, 130.2, 126.5, 105.7, 93.7, 81.8, 62.3, 47.7, 41.0, 38.8, 33.7, 29.4, 28.2, 27.8, 26.4. HRMS (M + Na) calcd 369.1309, found 369.1321. Anal. Calcd for C$_{19}$H$_{22}$O$_6$: C, 65.88; H, 6.40. Found: C, 65.29; H, 6.23.

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