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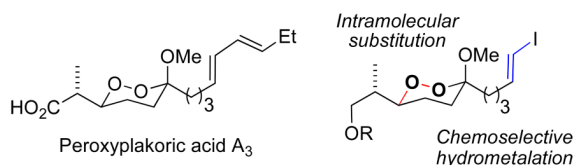
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## Asymmetric Synthesis of 1,2-dioxanes: Approaches to the Peroxyplakoric Acids

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### Abstract



The stereospecific intramolecular alkylation of a hydroperoxyacetal provides the basis for the first asymmetric synthesis of the dioxane propionate core of the peroxyplakorates. Chemoselective hydrometalation of an alkyne in the presence of a peroxide is used to introduce a synthon for the polyunsaturated side chains of the peroxyplakorates. The route suggests a general solution for the 1,2-dioxane unit in many peroxide natural products.

### Keywords

Peroxyplakoric; 1,2-dioxane; peroxide; intramolecular alkylation

### 1.0 Introduction

The peroxyplakoric acids are a family of marine natural products sharing a 6-methoxy-1,2-dioxane-3-propionic acid core,<sup>1, 2</sup> and differing in the stereochemistry at C<sub>3</sub> and in the geometry and substitution of the diene within the C<sub>6</sub> tail (Figure 1). Several members of the family, as well as some simplified analogs, possess significant antifungal or antimalarial activity.<sup>3,4</sup> However, there has been no reported synthesis of a peroxyplakoric acid,<sup>5</sup> nor has there been a general strategy for asymmetric synthesis of alkoxy-1,2-dioxanes.<sup>6</sup> We now report an asymmetric synthesis of 6-alkoxy-3,6-dialkyl-1,2-dioxanes by a route that should be broadly applicable to 1,2-dioxanes, one of the most common substructures in peroxide natural products.<sup>1,7,8</sup>

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## 2.0 Background

The two major challenges in the asymmetric synthesis of the peroxyplakorates are stereoselective introduction of the 3-alkoxy-3,6-dialkyl substituted 1,2-dioxane, and incorporation of both an oxidation-sensitive side chain and a reduction-sensitive 1,2-dioxane.

Most reported methods for the synthesis of 1,2-dioxanes involve electrophilic or radical cyclizations<sup>9,10,11</sup> and are, in general, poorly suited for an approach to the peroxyplakorates. However, the 1,2-dioxane propionate core can be formed through conjugate addition of a hydroperoxy enoate. This reaction, first observed by Bartlett and coworkers during investigations of intramolecular nucleophilic epoxidations,<sup>12</sup> was subsequently optimized for the synthesis of alkoxydioxanes,<sup>3</sup> and has been applied by several groups to the synthesis of simplified peroxyplakorate analogs.<sup>4</sup> However, a conjugate addition offers no obvious means of controlling the relative stereochemistry of the sidechain and dioxane stereocenters.<sup>13</sup> Furthermore, in the course of a recent total synthesis of structurally simpler peroxyacarnates,<sup>8,14</sup> we found that conjugate addition predominantly furnished the 1,2-dioxane isomer with C<sub>3</sub> and C<sub>6</sub> alkyl substituents in a *trans* (diequatorial) relationship; in the case of the peroxyplakorates, this would preclude any approach to the B-series of diastereomers. Finally, at the time these studies were initiated, conjugate addition offered no means for control of absolute stereochemistry, although a recent report on organocatalyst-mediated 5-*exo-trig* cyclizations of simple hydroperoxides offers some hope in this regard.<sup>15</sup>

The use of a conjugate addition also requires introduction of a hydroperoxyacetal nucleophile in presence of an enoate (Scheme 1). We found a reported acid-catalyzed peroxyacetalization<sup>3a</sup> to be very substrate dependent, something that has also been noted by others.<sup>4</sup> Model studies suggested that selective ozonolysis of a C<sub>6</sub>-methylene, a reaction we had successfully employed in the presence of a disubstituted enoate (Scheme 1, X = H),<sup>14</sup> was problematic in the presence of the trisubstituted enoate required for the peroxyplakorates (Scheme 1, X = CH<sub>3</sub>).

We became interested in a general approach to asymmetric synthesis of dioxanes based upon intramolecular nucleophilic substitution. Cyclization of a hydroperoxyepoxide has been applied to the asymmetric synthesis of the antimalarial Yingzhaosu A.<sup>16</sup> However, the homologous opening of secondary oxetanes proved unsuccessful.<sup>17</sup> These limitations led us to pursue intramolecular alkylations of hydroperoxyketals. We had previously observed the efficiency of intramolecular hydroperoxide alkylations in a 6-*exo tet* displacement of a primary iodide;<sup>18</sup> more recently, we employed a corresponding displacement of a secondary methanesulfonate as part of the synthesis of *spiro* bisperoxyacetals (Scheme 2).<sup>19</sup>

Our retrosynthetic approach (Scheme 3), illustrated for peroxyplakoric acid A<sub>3</sub>, is designed to allow a general solution to any member of the family. As the diene side chains in the peroxyplakorates are incompatible with ozonolytic introduction of the hydroperoxyacetal, we planned to employ Pd-mediated *sp*<sup>2</sup>/*sp*<sup>2</sup> couplings as a disconnect to a metalloalkene or iodoalkene.<sup>20</sup> What remained to be seen was whether the functionalized alkene could be installed via hydrometallation of an alkynyl-substituted dioxane. The 1,2-dioxane ring would be installed through a stereospecific intramolecular displacement of a secondary sulfonate by a hydroperoxyacetal, which would in turn be revealed through ozonolysis of an alkene. Our previous work with the peroxyacarnates had suggested that the terminal alkyne would be stable towards ozonolytic introduction of the hydroperoxyketal.<sup>8,14</sup> The secondary alcohol precursor of the sulfonate leaving group would be introduced via an asymmetric aldol reaction, with the choice of syn- or antiselective aldol determining the choice of peroxyplakoric A or B series.

Synthesis of the functionalized 1,2-dioxane core is illustrated in Scheme 4. As our initial target, we chose the peroxyplakorate “A” series. The 2,3-*syn* stereochemistry requires an *anti*-aldol precursor. The dialkylboronate derived from chiral ester **1**<sup>21</sup> underwent reaction with aldehyde **2**<sup>14</sup> to furnish a good yield of a mixture of aldol products in which the desired (2R,3R)-*anti* diastereomer (**3**) predominated; the only significant byproduct (8%) was the *syn*-2S,3R-diastereomer. Reduction of **3** to the 1,3-diol **4** was followed by selective protection of the primary alcohol to form the triisopropyl silyl ether (**5**). Although attempted activation of the C<sub>3</sub>-hydroxyl as the triflate resulted in significant decomposition, the corresponding mesylate **6** was easily prepared. Methanolic ozonolysis of the methylene group furnished a high yield of a 1:1 mixture of hydroperoxyacetals **7a** and **7b**, which were incompletely separated even by semipreparative HPLC and therefore carried on as a mixture.<sup>22</sup> Treatment with potassium *tert*-butoxide in the presence of 18-crown-6 furnished a 1:1 mixture of diastereomeric 1,2-dioxanes **8a** and **8b** in excellent yield. The configurational assignment of dioxane **8a** was based upon a combination of precedent for the aldol reaction, as well as the <sup>3</sup>J<sub>H</sub> constants for H<sub>3</sub> (11.0, 6.3, 1.9 Hz) in the <sup>1</sup>H NMR spectrum, which were very similar to the values reported for peroxyplakoric acids A<sub>1</sub>–A<sub>3</sub> and consistent with typical observations for 1,2-dioxane natural products bearing an axial hydrogen at C<sub>3</sub>.<sup>2, 23</sup> Interestingly, the undesired peroxyacetal **8b** failed to epimerize in the presence of mild acid and was decomposed by strong acid (for example, methanolic HCl).

Small quantities of the individual diastereomers **7a** and **7b** could be obtained by analytical HPLC. Subjecting the individual diastereomers to the cyclization conditions furnished the diastereomerically pure 1,2-dioxanes **8a** and **8b**, respectively, (Scheme 4) demonstrating that the cyclization was in fact stereospecific and allowing stereochemical assignment of the hydroperoxyacetals.

Chemoselective functionalization of the alkynyl dioxane to an *E*-iodoalkenyl dioxane was readily achieved by hydrozirconation with the Schwartz reagent, followed by quenching with iodine (Scheme 5). Our earlier studies had demonstrated the compatibility of dialkyl peroxides with a number of Pd-mediated *sp*<sup>2</sup>/*sp*<sup>2</sup> couplings,<sup>14,20,24</sup> Cross coupling of the alkenyl iodide **9** with an *E*-butenyl zinc reagent derived from hydrozirconation of 1-butyne furnished a nearly inseparable 1:3 mixture of the desired diene and the terminal alkene derived from a net reduction.<sup>25</sup> A small amount of diene, separated through careful chromatography, was treated with fluoride to reveal **12**, the primary alcohol precursor of the peroxyplakorate A<sub>3</sub>.

### 3. Conclusion

We have demonstrated an approach to the peroxyplakoric acid family of 1,2-dioxanes by a route, which, through choice of aldol precursor or the organometallic coupling partner, should be applicable to any member of the peroxyplakorates. The stereospecific intramolecular alkylation at the heart of the approach suggests a new and broadly applicable asymmetric approach to 1,2-dioxane natural products which include a secondary peroxide linkage;<sup>1,6</sup> two examples are shown below (Figure 2).<sup>26,27</sup>

## 4. Experimental

### 4.1 General Procedures

Dichloromethane and THF were distilled from CaH<sub>2</sub> and Na/benzophenone, respectively. All other reagents were used as received, except as noted. All reactions were conducted under an atmosphere of nitrogen except where noted. Thin layer chromatography (TLC) was performed on 0.25 mm hard-layer silica G plates; developed plates were visualized with UV lamp and/or by staining: 1% ceric sulfate and 10% ammonium molybdate in 10% H<sub>2</sub>SO<sub>4</sub> (general stain, after charring); 1% *N,N'*-dimethyl-*p*-phenylenediamine solution in 1:20:100 acetic acid/water/

methanol (specific for peroxides);<sup>28</sup> 1% aq. KMnO<sub>4</sub> (for unsaturated compounds). “Standard drying and purification (solvent)” refers to drying of organic extracts over Na<sub>2</sub>SO<sub>4</sub>, removal of solvent under vacuum, and purification by flash chromatography using the indicated eluting solvent. Analytical HPLC was performed on a 4.6 mm × 25 cm Si column (5 μm); semi-preparative HPLC on a 21.4 mm × 25 cm Si column (8 μm); both employed RI detection. <sup>1</sup>H, and <sup>13</sup>C spectra were recorded at 300, 400, or 500 MHz in CDCl<sub>3</sub> unless otherwise indicated; peaks are reported as: chemical shift (number of protons, multiplicity, J couplings in Hz). Infrared spectra were recorded as neat ATR films with selected absorbances reported in wavenumbers (cm<sup>-1</sup>). Optical rotations were measured on a digital polarimeter at ambient temperature.

#### 4.2 (1R, 2S)-2-(N-Benzyl-N-mesitylenesulfonyl)amino-1-phenyl-1-propyl, propionate ester (1)

was prepared in three steps from norephedrine by a slight variant of the reported procedure in which the crude propionate **1** was not triturated with hexane but directly recrystallized from EA/Hex.<sup>21</sup>

#### 4.3 4-Methylenenon-8-ynal (2)

was prepared in three steps from 5-hexynoic acid by the method described in Xu, et al.<sup>14</sup> The volatile and sensitive aldehyde was used without purification: <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 9.6 (1 H, t, *J* = 1.6 Hz), 4.6-4.5 (2 H, m), 2.39 (2 H, dt, *J* = 1.6 Hz and 7.6 Hz), 2.1 (2 H, br t, *J* = 7.5 Hz), 1.99 (2 H, dt, *J* = 2.6 and 7.1 Hz), 1.94 (2 H, br t, *J* = 7.9 Hz), 1.8 (1H, t, *J* = 2.6 Hz), 1.5-1.4 (2 H, m but overall quintet *J* ~ 7.4 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 201.9, 146.6, 110.1, 84.0, 68.7, 41.7, 35.0, 27.9, 26.3, 17.8.

#### 4.4 Dicyclohexyl(trifluoromethylsulfonyloxy)borane

was prepared by a slight modification of the method of Inoue, et al,<sup>21</sup> in which the biphasic obtained by allowing the crude reaction mixture to stand was separated by withdrawal of the lower phase with a syringe and needle.

#### 4.5 (2R, 3R) [(1R, 2S)-2-(N-Benzyl-2,4,6-trimethylphenylsulfonamido)-1-phenylpropyl] 3-hydroxy-2-methyl-6-methyleneundec-10-ynoate (3)

was prepared from the chiral propionate **1** and aldehyde **2** by a variant of the method of Inoue, et al.<sup>21</sup> Into an oven-dried 250 mL round bottom flask under nitrogen was added (1R, 2S)-2-(N-Benzyl-N-mesitylenesulfonyl) amino-1-phenyl-1-propyl propionate (3.1 g, 6.5 mmol) and 40 mL CH<sub>2</sub>Cl<sub>2</sub>. To this solution was added Et<sub>3</sub>N (2.2 mL, 16 mmol) via syringe. The solution was cooled to -78 °C and a solution of dicyclohexylboron triflate (1.0M in hexane, 13 mL, 13 mmol) was added dropwise over 15 minutes. The resulting solution was stirred at -78 °C for 2h. Crude 4-methylenenon-8-ynal (1.2 g, 7.9 mmol) in 5 mL CH<sub>2</sub>Cl<sub>2</sub> was added dropwise to the enol boronate solution. The reaction mixture was stirred for 1 hr at -78 °C and was allowed to warm to room temperature over 1h, then quenched by addition of 0.1 M pH 7 phosphate buffer solution (24 mL). The mixture was diluted with 120 mL methanol, after which, 30% H<sub>2</sub>O<sub>2</sub> (12 mL) was added carefully. The resulting suspension was stirred vigorously overnight and then concentrated. The residue was partitioned between water (50 mL) and CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (75 mL × 2). The combined organic layers were washed with water (60 mL × 3) and dried with Na<sub>2</sub>SO<sub>4</sub>. The filtered organic layer was concentrated and the residue was purified by flash chromatography using 15%–25% EA/Hex as the eluting solvent to afford **4** as a clear oil which solidified just below room temperature. Yield: 3.51 g, 86%; *R*<sub>f</sub> = 0.33 (25% EA/Hex); [α]<sub>D</sub> = 19.5 (c 0.87, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.15 (3H, d, *J* = 7.3Hz), 1.19 (3H, d, *J* = 7.0 Hz), 1.49–1.69 (4H, m), 1.95 (1H, t, *J* = 2.6 Hz), 2.03–2.25 (4H, m), 2.18 (2H, td, *J* = 7.1 and 2.6 Hz), 2.28 (3H, s), 2.43–2.52 (1H, m), 2.49 (6H, s), 2.55 (1H, d, *J* = 6.8 Hz), 3.61–3.67 (1H, dtd, *J* = 3.5, 6.8, 9.5 Hz), 4.11–4.15

(1H, dq, 4.0 and 6.9 Hz), 4.54 (1H, B of AB,  $J_{AB} = 16.5$  Hz), 4.75 (1H, A of AB,  $J_{AB} = 16.5$  Hz), 4.75 (2H, s), 5.86 (d, 1H), 6.87 (2H, s), 6.88–6.90 (2H, m), 7.17–7.30 (8H, m);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  174.5, 148.2, 142.6, 140.3, 138.4, 138.2, 133.4, 132.1, 128.5, 128.4, 128.0, 127.7, 127.2, 126.0, 109.9, 84.3, 78.3, 72.8, 68.5, 56.8, 48.2, 45.5, 35.0, 32.4, 31.8, 26.5, 23.0, 21.0, 18.0, 14.1, 13.5; IR: 3532, 3299, 3031, 2981, 2942, 1737, 1604, 1454, 1381, 1321, 1153, 1013, 858, 757, 699, 659; MS: HR-FAB: calcd. for  $\text{C}_{38}\text{H}_{47}\text{NO}_5\text{S}$   $[\text{M}+\text{Li}]^+$ : 636.3334, Found: 636.3346.

#### 4.7 (2S, 3R)-2-Methyl-6-methyleneundec-10-yne-1,3-diol (4)

To a stirred solution of the chiral ester **3** (2.6 g, 4.2 mmol) in THF (40 mL) was added lithium aluminum hydride (0.19 g, 5.0 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1h and then quenched by the careful addition of  $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$ . The mixture was stirred vigorously for 30 minutes and filtered. The residue obtained upon concentration was resuspended in hexane (60 mL) and then filtered, resulting in recovery of the auxiliary alcohol. The residue obtained upon concentration of the filtrate was separated by chromatography with 1:1 ethyl acetate and hexane to afford the 1,3-diol **5** as a clear colorless oil. Yield: 0.64 g, 73%;  $R_f = 0.27$  (50%EA/Hex);  $[\alpha]_D = 31.7$  (c 1.1,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  4.79 (1H, s), 4.77 (1H, s), 3.77 (1H, dd,  $J = 3.7$  and 10.8 Hz), 3.55–3.64 (2H, m), 2.90 (2H, br s), 2.04–2.22 (6H, m), 1.95 (1H, t,  $J = 2.6$  Hz), 1.53–1.77 (5H, m), 0.89 (3H, d,  $J = 7.0$  Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  148.6, 109.7, 84.3, 76.9, 68.5, 67.5, 39.8, 34.8, 33.2, 31.7, 26.4, 17.9, 13.8; IR: 3302 (br), 2939, 1644, 1432, 1275, 1026; MS: HR-FAB: calcd. for  $\text{C}_{13}\text{H}_{22}\text{O}_2$ :  $[\text{M}+\text{Li}]^+$ : 217.1780, Found: 217.1778.

#### 4.8 (2S, 3R)-2-Methyl-6-methylene-1-(triisopropylsilyloxy)undec-10-yn-3-ol (5)

Diol **4** (0.55 g, 2.6 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (15 mL) and cooled to 0 °C. To this solution was added  $\text{Et}_3\text{N}$  (0.44 mL, 3.2 mmol), DMAP (32 mg, 0.26 mmol), and triisopropylsilyl chloride (0.61 mL, 2.9 mmol) sequentially. This mixture was warmed to room temperature and stirred for 15h, and then quenched with saturated aq.  $\text{NH}_4\text{Cl}$ . The aqueous phase was extracted with  $\text{Et}_2\text{O}$ , and the combined organic extracts were dried with  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated *in vacuo*. The resulting crude material was purified by column chromatography using 5% EA/Hex to afford 0.81 g of the silyl ether as colorless oil. Yield 85%;  $R_f = 0.44$  (10% EA/Hex);  $[\alpha]_D = 25.1$  (c 1.2,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.85 (3H, d,  $J = 7.0$  Hz), 1.03–1.15 (21H), 1.49–1.76 (5H), 1.92 (1H, t,  $J = 2.6$  Hz), 2.02–2.29 (6H, m), 3.54 (1H, m), 3.66 (1H, dd,  $J = 7.7$  and 9.9 Hz), 3.88 (1H, dd,  $J = 3.9$  and 9.9 Hz), 3.97 (1H, d, 3.0 Hz), 4.72 (1H, s), 4.76 (1H, s);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  148.9, 109.2, 84.4, 76.5, 69.1, 68.3, 39.6, 35.1, 33.4, 31.5, 26.5, 17.94, 17.89, 13.7, 11.7; IR: 3439 (br), 3314, 2943, 2886, 1645, 1463, 1386, 1276, 1261, 1062, 996, 883, 797; MS: HR-FAB: calcd. for  $\text{C}_{22}\text{H}_{42}\text{O}_2\text{Si}$ :  $[\text{M}+\text{H}]^+$ : 367.3033, Found: 367.3042.

#### 4.9 (2S,3R)-2-Methyl-6-methylene-1-(triisopropylsilyloxy)undec-10-yn-3-yl methanesulfonate (6)

Alcohol **5** (0.70 g, 1.9 mmol) was dissolved in  $\text{CH}_2\text{Cl}_2$  (10 mL) and the solution was cooled to 0 °C.  $\text{Et}_3\text{N}$  (0.32 mL, 2.3 mmol) and  $\text{MsCl}$  (0.18 mL, 2.3 mmol) were added and the reaction mixture was allowed to warm to room temperature. After stirring for 14 h, the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and then washed with sat. aq.  $\text{NH}_4\text{Cl}$  and brine and dried with  $\text{Na}_2\text{SO}_4$ . The crude mesylate obtained upon concentration was purified by chromatography (10% EA/Hex) to afford 0.69 g of mesylate **6**. Yield: 0.69 g, 81%;  $R_f = 0.26$  (10% EA/Hex);  $[\alpha]_D = 7.0$  (c 0.97,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  0.97 (3H, d,  $J = 7.0$  Hz), 1.04–1.11 (21H), 1.62–1.1.70 (2H), 1.77–1.89 (2H), 1.94 (1H, t,  $J = 2.6$  Hz), 2.03–2.27 (7H), 3.00 (3H, s), 3.63 (1H, s), 3.65 (1H, s), 4.78 (2H, s), 4.89 (1H, dt,  $J = 3.9$  and 8.8 Hz);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  147.5, 110.1, 85.1, 84.2, 68.5, 65.0, 39.7, 38.6, 34.9, 31.6, 28.4, 26.5, 18.0, 17.7, 11.9, 11.6; IR: 3312,

2943, 2893, 2866, 1646, 1463, 1336, 1175, 1109, 908, 884, 795, 678.; MS: HR-FAB: calcd. for  $C_{23}H_{44}O_4SSi$ : $[M+H]^+$ : 445.2809, Found:445.2805.

#### 4.10 6-Hydroperoxy-6-methoxy-2-methyl-1-(triisopropylsilyloxy)undec-10-yn-3-ylmethanesulfonate (**7a** and **7b**)

A stream of  $O_3/O_2$  was bubbled into a  $-78^\circ C$  solution of mesylate **7** (0.82 g, 1.8 mmol) in 15 mL methanol and 50 mL  $CH_2Cl_2$  until the starting material had disappeared (TLC). The reaction was sparged with  $N_2$  and then allowed to warm to room temperature and concentrated in *vacuo*. The residue was purified through a short flash column using 30% EA/Hex to afford 0.77 g (88%) of a 1:1 mixture of diastereomers **7a** and **7b**. Yield: 0.77 g, 88%.  $R_f$  = 0.27 (33% EA/Hex).  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  108.2, 108.0, 84.8, 84.3, 83.8, 83.7, 77.2, 77.3, 69.0, 68.9, 48.7, 48.6, 39.6, 39.2, 38.7, 38.5, 29.6, 29.0, 27.0 24.8 24.6, 22.61, 22.60, 18.41, 18.40, 18.0, 12.1, 11.9, 11.8; HRFABMS calcd. for  $C_{23}H_{46}O_7SSi$ :  $[M-HO_2]^+$ : 461.2675, Found: 461.2765.

Small quantities of pure diastereomers could be separated by analytical HPLC (EA/Hex):<sup>22</sup> **7a** (2S, 3R, 6R);  $^1H$  NMR ( $CDCl_3$ )  $\delta$  7.61 (1H, s), 4.87–4.91 (1H, m), 3.68 (1H, s), 3.66 (1H, s), 3.32 (3H, s), 3.04 (3H, s), 2.18–2.28 (3H, m (contains 2H, dt,  $J$  = 2.6 and 6.7 Hz at 2.27 ppm)), 1.99 (1H, t,  $J$  = 2.6 Hz), 1.90–1.98 (1H, m), 1.72–1.82 (5H, m), 1.50–1.63 (3H, m), 1.03–1.14 (21H, m), 0.98 (3H, d,  $J$  = 7.0 Hz). **7b** (2S, 3R, 6S);  $^1H$  NMR ( $CDCl_3$ )  $\delta$  8.08 (1H, s), 4.91–4.95 (1H, m), 3.69 (1H, s), 3.68 (1H, s), 3.34 (3H, s), 3.05 (3H, s), 2.14–2.28 (3H, m (contains 2H, dt,  $J$  = 2.6 and 6.7 Hz at 2.26 ppm)), 1.88–2.0 (3H, m (contains 1H, t,  $J$  = 2.6 Hz)), 1.66–1.80 (4H, m), 1.50–1.63 (3H, m), 1.03–1.14 (21H, m), 0.98 (3H, d,  $J$  = 7.0 Hz).

#### 4.11 (2S)-1-Triisopropylsiloxy-2-((3S, 6R)-6-methoxy-6-(pent-4-ynyl)-1,2-dioxan-3-yl)propane (**8a**)

To a solution of hydroperoxy acetal (**7a**) (17.3 mg, 0.03 mmol) in anhydrous toluene (0.4 mL) was added 18-crown-6 (9.5 mg, 0.04 mmol), followed by  $KOt$ -Bu (5.8 mg, 0.05 mmol). The reaction mixture was stirred for 20 minutes, at which point additional  $KOt$ -Bu (3.3 mg, 0.03 mmol) was added. After stirring for an additional 20 min, the reaction became yellow, and TLC indicated the absence of starting material. The crude reaction mixture was filtered through a short pad of silica gel with 20% EA/Hex. The filtrate was concentrated and the residue was purified by column chromatography using 5% EA/Hex to afford dioxane **8a**. Yield: 11.3 mg, 79%;  $R_f$  = 0.36 (5% EA/Hex);  $[\alpha]_D = -144$  (c 0.74,  $CHCl_3$ );  $^1H$  NMR ( $CDCl_3$ ):  $\delta$  4.05 (1H, ddd,  $J$  = 1.9, 6.3, 11.0 Hz), 3.68 (1H, dd,  $J$  = 5.2 and 9.8 Hz), 3.63 (1H, dd,  $J$  = 5.6 and 9.8 Hz), 3.28 (3H, s), 2.19–2.24 (2H, m), 1.96 (1H, t,  $J$  = 2.6 Hz), 1.41–1.92 (9H, m), 1.03–1.13 (21H, m), 1.01 (3H, d,  $J$  = 6.9 Hz);  $^{13}C$  NMR ( $CDCl_3$ ):  $\delta$  102.3, 83.8, 81.7, 68.8, 65.1, 48.4, 39.7, 31.9, 30.7, 22.9, 22.1, 18.5, 18.0, 12.7, 12.0; IR: 3312, 2943, 2866, 1462, 1238, 1109, 1066, 917, 882, 789, 746, 682; MS: HR-FAB: calcd. for  $C_{22}H_{42}O_4Si$ : $[M+Li]^+$  405.3012, Found: 405.3000.

#### 4.12 (2S)-1-Triisopropylsiloxy-2-((3S, 6S)-6-methoxy-6-(pent-4-ynyl)-1,2-dioxan-3-yl)propane (**8b**)

By a similar procedure, hydroperoxy acetal (**7b**) (20 mg, 0.04 mmol) was converted to 1,2-dioxane **8b**. Yield: 14.5 mg, 87%;  $R_f$  = 0.36 (5% EA/Hex);  $[\alpha]_D = +121.4$  (c 1.4,  $CHCl_3$ );  $^1H$  NMR ( $CDCl_3$ )  $\delta$  3.93 (1H, dt,  $J$  = 8.5 and 5.7 Hz), 3.70 (1H, dd,  $J$  = 4.7 and 9.9 Hz), 3.67 (1H, dd,  $J$  = 4.7 and 8.8 Hz), 3.34 (3H, s), 2.25 (2H, dt, 2.6 and 6.7 Hz), 2.03–2.15 (2H, m), 1.99 (1H, t,  $J$  = 2.6 Hz), 1.75–1.86 (2H, m), 1.54–1.74 (5H, m), 1.12 (3H, d,  $J$  = 6.8 Hz), 1.04–1.10 (21H, m);  $^{13}C$  NMR ( $CDCl_3$ )  $\delta$  102.3, 83.8, 81.7, 68.8, 65.1, 48.4, 39.7, 31.9, 30.7, 22.9, 22.1, 18.5, 18.0, 12.7, 12.0; IR: 3312, 2943, 2866, 1462, 1238, 1109, 1066, 917, 882, 789, 746, 682; MS: HR-FAB: calcd. for  $C_{22}H_{42}O_4Si$ : $[M+Li]^+$  405.3012, Found: 405.3000.

**4.13 One Pot Ozonolysis/Cyclization Method: (2S)-1-Triisopropylsiloxy-2-((3S, 6R)-6-methoxy-6-(pent-4-ynyl)-1,2-dioxan-3-yl)propane (8b)**

Mesylate **6** (0.6811 g, 1.5 mmol) was dissolved in 20 mL CH<sub>2</sub>Cl<sub>2</sub> and methanol (7.8 mL, 193 mmol). The solution was cooled to -78 °C and treated with a stream of O<sub>3</sub>/O<sub>2</sub>. The reaction was monitored by TLC until starting material was absent. The reaction mixture was then sparged with nitrogen and allowed to warm to room temperature. To this solution was added 18-Crown-6 (396.8 mg, 1.5 mmol), followed by KO<sup>t</sup>-Bu (154.2 mg, 1.4 mmol). The reaction mixture was stirred for 20 minutes, at which point additional KO<sup>t</sup>-Bu (170.5 mg, 1.5 mmol) was added. After stirring for an additional 20 min, the reaction became yellow, and TLC indicated the absence of starting material. The crude reaction mixture was filtered through a short pad of silica gel with 20% EA/Hex. The filtrate was concentrated and the residue was purified by column chromatography using 5% EA/Hex to afford 458.4 mg (75%) of an approximately 1:1 mixture of **8a** and **8b**. Yield: 75%.

**4.14 (2S)-1-Triisopropylsiloxy-2-((3S,6R)-6-methoxy-6-((4E)-4-iodopent-4-enyl)-1,2-dioxan-3-yl) propane (9)**

1,2-Dioxane **8a** (0.43 g, 1.1 mmol), azeotropically dried by concentration from distilled toluene (2×15 mL), was dissolved in 10 mL dry toluene. To this solution was added Cp<sub>2</sub>ZrHCl (0.38 g, 1.5 mmol) under a nitrogen atmosphere. After stirring for 15 minutes, the solution became light orange in color. Another portion of Cp<sub>2</sub>ZrHCl (0.21 g, 0.8 mmol) was added and the reaction mixture was stirred for another 15 minutes. Iodine (0.41 g, 1.6 mmol) was added slowly until the dark red color became permanent. The reaction mixture was diluted with 50 mL Hex, and filtered through Celite. The filtrate was washed with saturated aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, dried with Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified by column chromatography using 5–10% EA/Hex to afford 0.43 g (76%) of a 1:3 mixture of the terminal alkene reduction product (due to water) and the desired terminal E-iodoalkene **9** which could be separated by semi-prep HPLC (EA/Hex). *R*<sub>f</sub> = 0.32 (5% EA/Hex); [α]<sub>D</sub> = -97.2 (c 0.94, CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 6.48 (1H, dt, *J* = 14.4 and 7.1 Hz), 6.01 (1H, dt, *J* = 14.4 and 1.3 Hz), 4.01–4.06 (1H, m), 3.67 (1H, dd, *J* = 5.2 and 9.9 Hz), 3.63 (1H, dd, *J* = 5.6 and 9.9 Hz), 3.24 (3H, s), 2.03–2.08 (2H, m), 1.82–1.92 (2H, m), 1.24–1.67 (7H, m), 1.03–1.12 (21H, m), 1.00 (3H, d, *J* = 6.9 Hz); <sup>13</sup>C NMR (CDCl<sub>3</sub>) δ 145.7, 102.3, 81.7, 75.2, 65.0, 48.4, 39.6, 36.0, 32.1, 30.7, 22.9, 21.8, 18.0, 12.7, 11.9; IR: 2942, 2865, 1462, 1234, 1110, 1070, 1030, 946, 882, 788, 683, 659; MS: HRFAB: calcd. for C<sub>22</sub>H<sub>43</sub>LiO<sub>4</sub>Si:[M+Li]<sup>+</sup> 533.2136, Found: 533.2125.

**4.11 (2S)-1-Triisopropylsiloxy-2-((3S,6R)-6-methoxy-6-((4E,6E)-nona-4,6-dienyl)-1,2-dioxan-3-yl) propane (10)**

1-Butyne (0.12 g, 2.2 mmol) was condensed into a 50 mL flask at -78 °C under a N<sub>2</sub> atmosphere, and dissolved in distilled THF (4 mL) and distilled toluene (4 mL). The solution was warmed slowly to 0 °C, whereupon Cp<sub>2</sub>ZrHCl (0.22 g, 0.85 mmol) was added. The reaction was held at 0 °C for one hour, after which another portion of Cp<sub>2</sub>ZrHCl (0.10 g, 0.39 mmol) was added. The reaction mixture was stirred for another hour at 0 °C then the ice bath was then removed. After 10 minutes, the solution was cooled to 0 °C again and ZnCl<sub>2</sub> (0.12 g, 0.88 mmol) in 2 mL dry THF was added.<sup>25</sup> The reaction solution turned orange and was stirred at 0 °C for 10 minutes. Vinyl iodide **9** (0.16 g, 0.30 mmol) was added, followed by Pd(PPh<sub>3</sub>)<sub>4</sub> (45 mg, 0.04 mmol). The reaction was stirred at 0 °C for 5 minutes. TLC indicated the presence of significant amount of starting material, and another portion of Pd(PPh<sub>3</sub>)<sub>4</sub> (15 mg, 0.01 mmol) was added. The reaction mixture was stirred at 0 °C for an additional 0.5 h, at which point TLC indicated the absence of starting material. The reaction was diluted with 20 mL hexane, and the reaction mixture was filtered through a short pad of silica gel with 30% EA/Hex. The filtrate was concentrated in *vacuo* and the residue was purified by flash chromatography (5% EA/Hex)

to give 0.13 g of an inseparable mixture of diene **10** and terminal alkene **11**. The coupled and reduced products were separable after removal of the TIPS ether (next step).

#### 4.12 ((2S)-2-((3S, 6R)-6-Methoxy-6-((4E, 6E)-nona-4,6-dienyl)-1,2-dioxan-3-yl) propan-1-ol (12)

A few mg of the mixture of diene and terminal alkene from the previous step was dissolved in THF. A solution of TBAF (nominally 1M in THF) was added dropwise until TLC indicated the disappearance of the starting material. The reaction mixture was washed with saturated ammonium chloride solution and water sequentially. Then the separated organic layer was dried with Na<sub>2</sub>SO<sub>4</sub>, concentrated. The residue was first purified by flash chromatography, and then by HPLC. The desired deprotected diene product was very easily isolated by HPLC. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 5.95–6.06 (2H, m), 5.49–5.66 (2H, m), 4.10–4.14 (1H, m), 3.54–3.70 (m, 2H), 3.25 (3H, s), 2.04–2.20 (4H, m), 1.82–2.01 (3H, m), 1.25–1.72 (6H, m), 0.99 (3H, t, *J* = 7.4 Hz), 0.96 (3H, d, *J* = 7.2 Hz); <sup>13</sup>C δ 134.5, 131.2, 131.0, 129.1, 102.8, 82.4, 65.1, 48.4, 39.1, 32.5, 32.2, 30.5, 25.6, 22.7, 21.6, 13.6, 11.9; HRFABMS calcd. for C<sub>17</sub>H<sub>30</sub>O<sub>4</sub>Li:[M+Li]: 305.2304; Found: 305.2305 (0.2 ppm).

### Acknowledgments

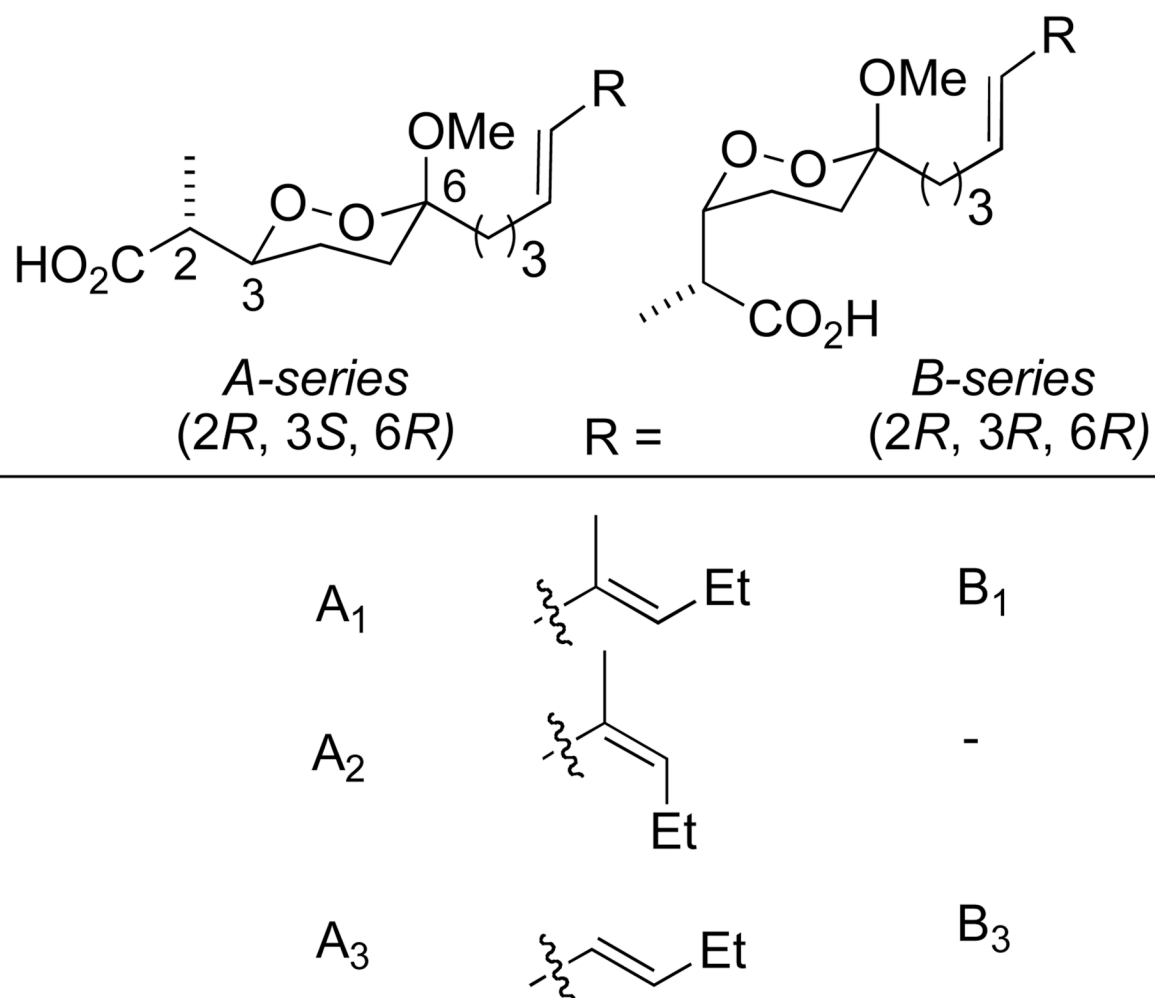
Research was conducted in facilities remodeled with support from NIH (RR016544-01). NMR spectra were acquired, in part, on spectrometers purchased with NSF support (MRI 0079750 and CHE 0091975). We thank Dr. Don Davies and Ms. Laure Chauset for some initial experiments related to alkylation of hydroperoxyacetals, and Ms. Carita Kordik for assistance with mass spectrometry.

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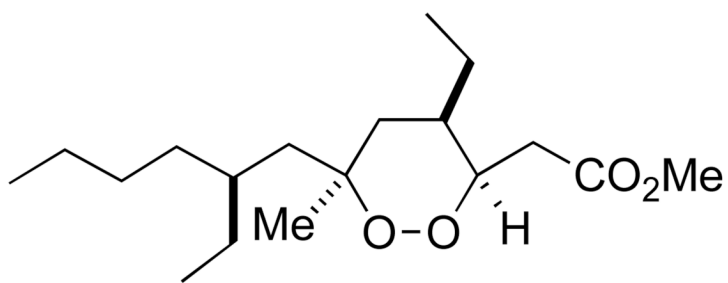
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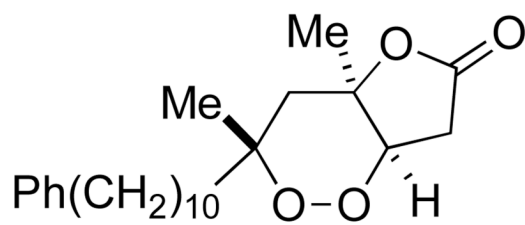
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**Figure 1.**  
Peroxyplakoric acids



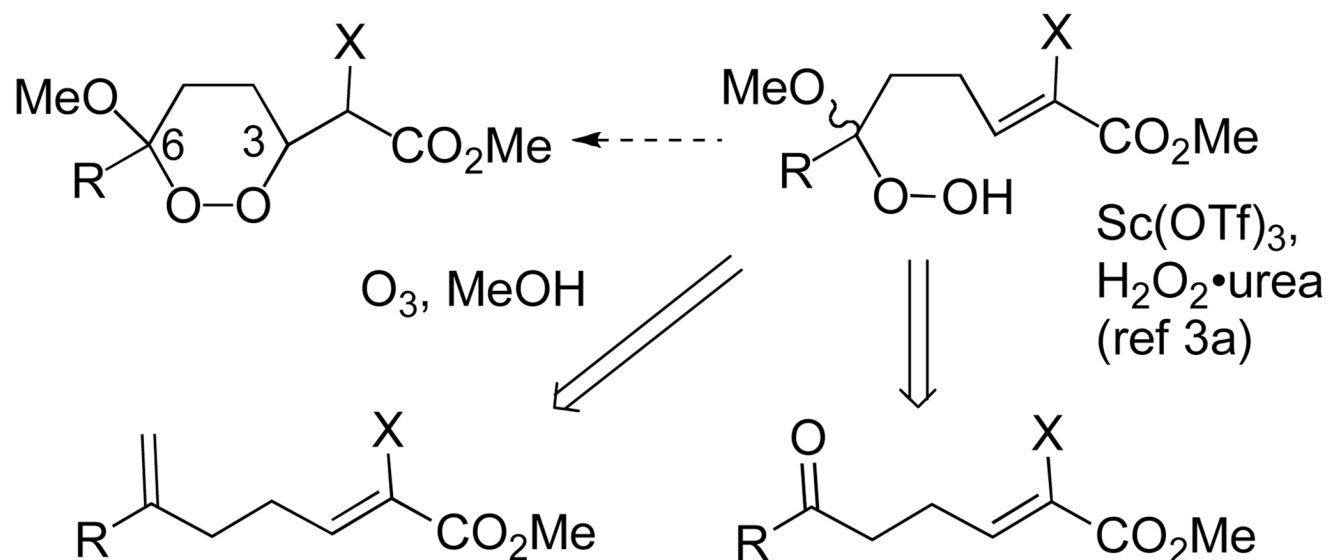
Plakortin (ref. 26)



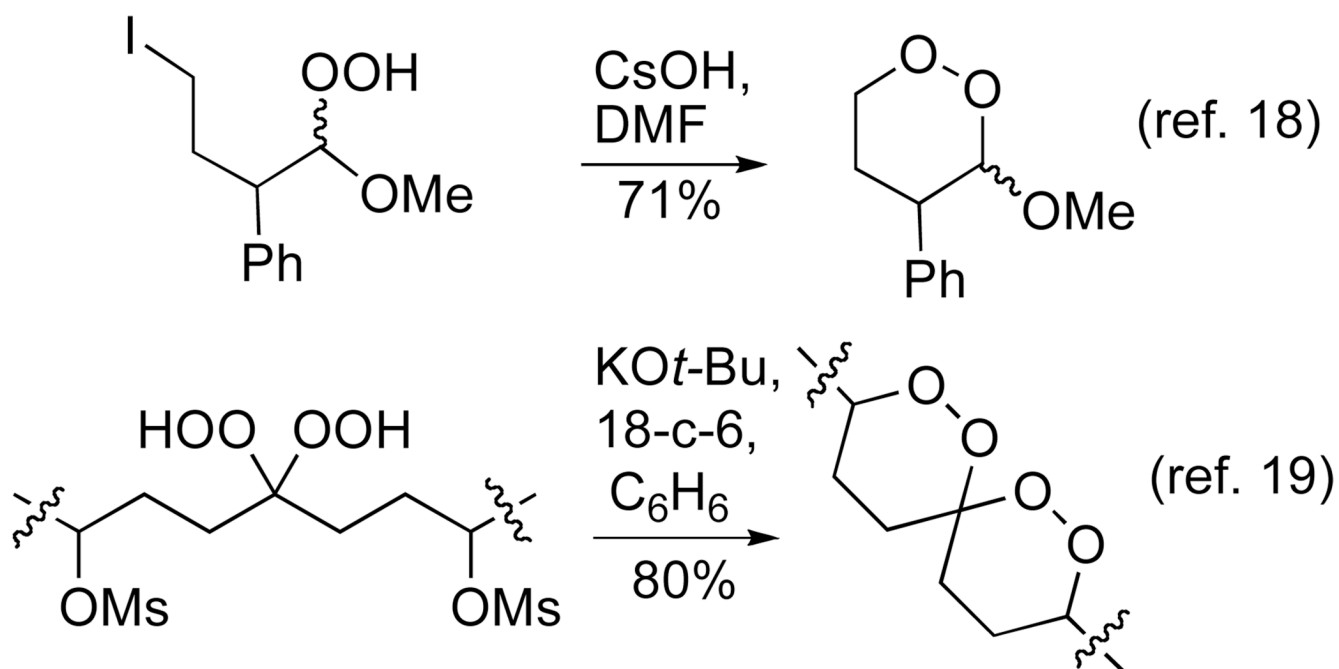
Plakortolide E (ref. 27)

**Figure 2.**  
1,2-dioxanes with secondary peroxide elements

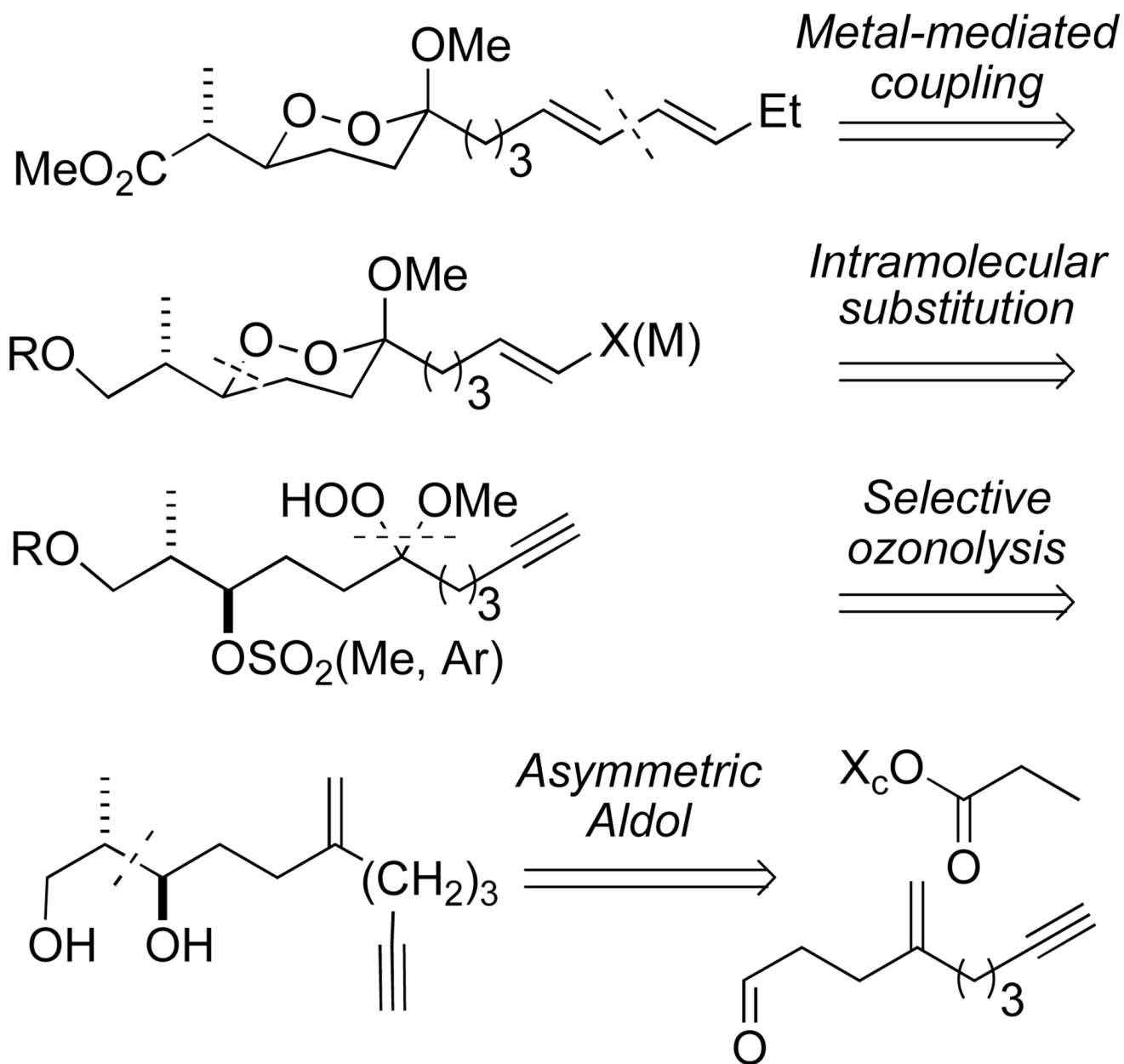
Peroxyacarnates (X = H) vs.  
peroxyplakorates (X = Me)



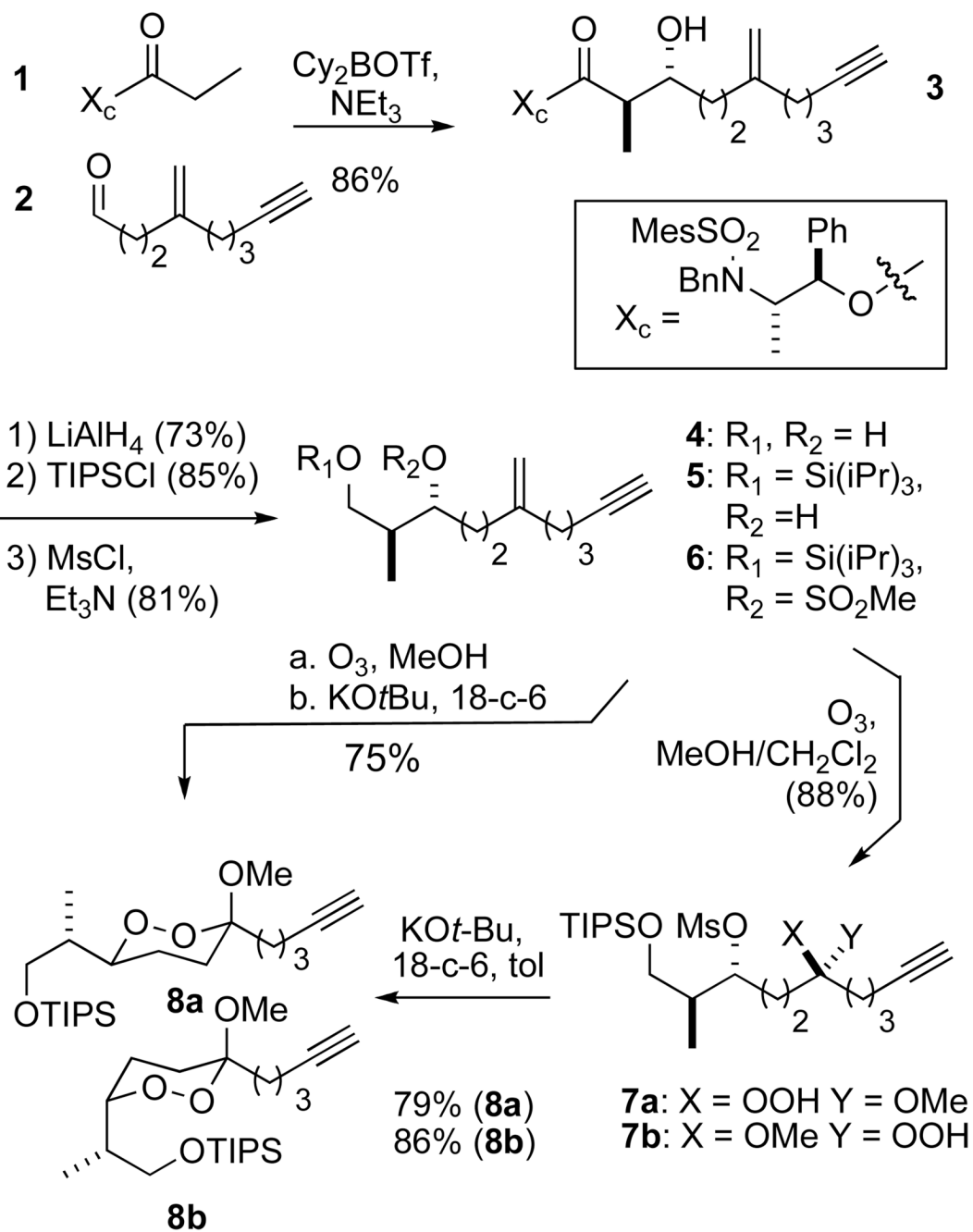
**Scheme 1.**  
Methods for introduction of the hydroperoxyacetal



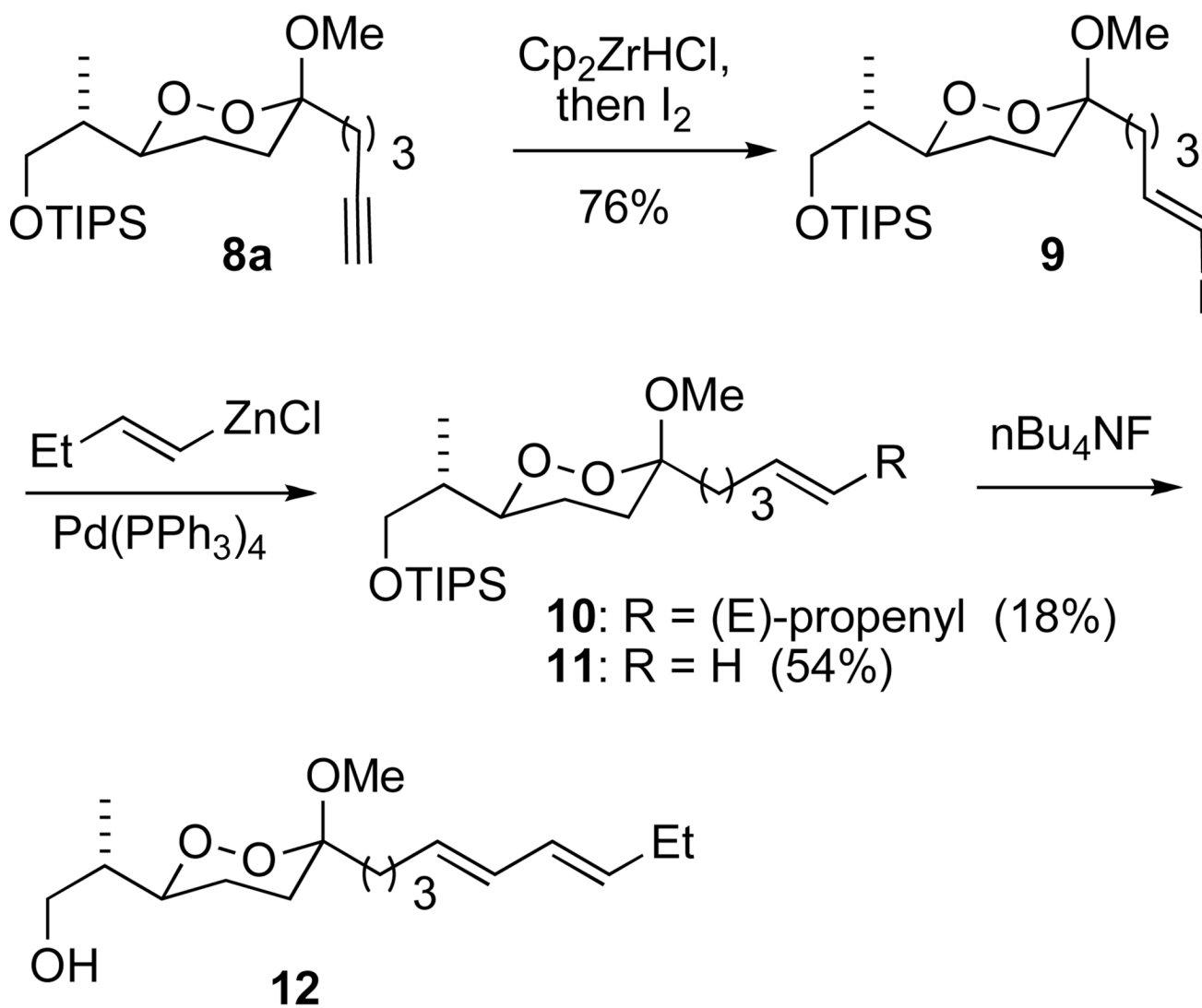
**Scheme 2.**  
Intramolecular displacements with hydroperoxyacetals



**Scheme 3.**  
Retrosynthesis of Peroxyplakorate A<sub>3</sub>



**Scheme 4.**  
Dioxane core synthesis



**Scheme 5.**  
Negishi coupling