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Synthesis of oxetane-3-carboxaldehyde and methyl oxetane-3-carboxylate via homologation of oxetane-3-one

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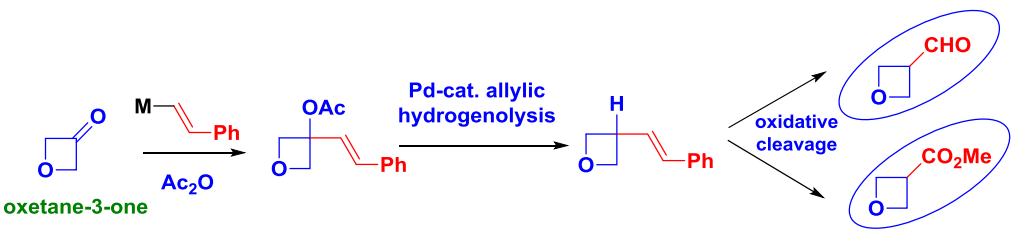
A 4-pot telescoped procedure to prepare oxetane-3-carboxaldehyde and methyl oxetane-3-carboxylate was developed using readily available starting materials. Classical homologation methods applied to oxetane-3-one proved challenging due to the sensitivity of the oxetane ring toward strongly oxidative, basic and acidic conditions. Subsequently, a mild homologation sequence was developed. The key steps involve a Tsuji hydrogenolysis of an allylic acetate, osmium-free dihydroxylation and oxidative cleavage. Although methyl oxetane-3-carboxylate is marketed by a small number of specialty chemical companies, this work represents the first published preparation of this vital building block.



1. Introduction

Oxetanes are important heterocycles for drug discovery as demonstrated by Carreira[1–14] and others.[15,16] Modification of a lipophilic or poorly soluble lead compound by the incorporation of an oxetane can positively impact the physiochemical properties of that lead. For example, improved aqueous solubility and metabolic stability were gained by judicious substitution of an oxetane in place of larger cyclic ethers in a program focused on γ-secretase inhibitors.[17] Oxetanes have also appeared in natural products with biological activity, the Taxane family being the most well-known (Fig. 1).

Because of their symmetry, 3-substituted oxetanes are particularly important since they do not introduce the complexity of a new chiral center. A large body of excellent synthetic work has focused on 3,3-disubtituted and 2-substituted oxetanes but fewer literature reports describe methods to prepare 3-monosubstituted oxetanes. Due to ring strain and the basicity of the oxygen, oxetanes can undergo ring opening reactions under acidic conditions to form allylic and homo-allylic alcohols.[18–20] Strategic ring opening, ring expansion and C2 functionalization of oxetanes can afford a variety of oxygen containing heterocycles. For oxetane containing lead compounds, the ring opening reaction is an undesired event complicating synthesis of these important heterocyclic compounds.[21] To circumvent these complications, synthesis of 3-monosubstituted oxetanes tend to be lengthy. For example, the synthesis of oxetane-3-methanol takes 7 steps with an overall yield of 12%.[22] This process is stymied by four protection/deprotection steps and a low yielding oxetane ring formation step. The targets of this report have a 3-carbonyl group and 3-hydrogen making ring opening reactions via beta-elimination a facile process, due to activation of beta-elimination by the carbonyl. This

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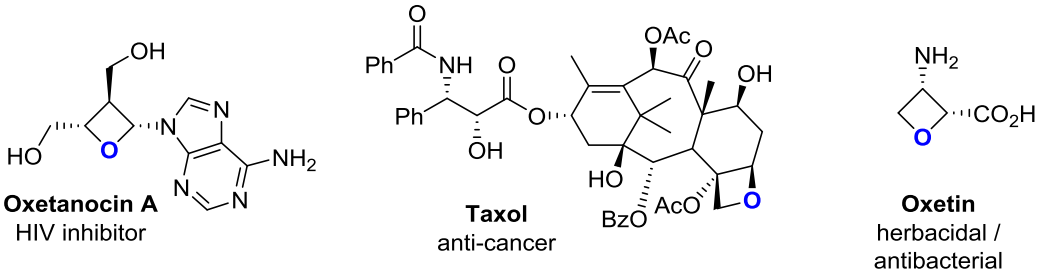
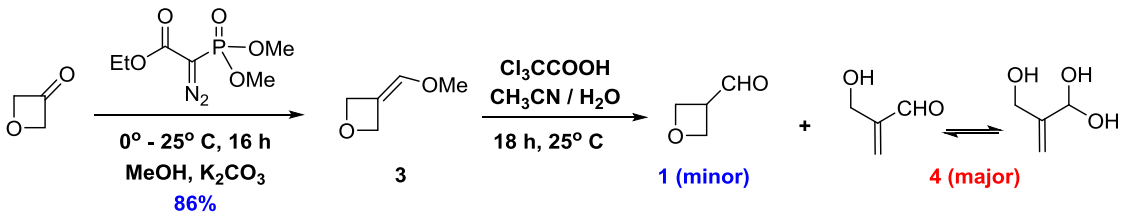


Fig. 1. Examples of oxetane rings in natural products.

structural feature makes synthesis of these simple looking building blocks more complicated than one might anticipate. The basic form 2-(hydroxymethyl)acrylaldehyde **4** as a mixture of aldehyde and hydrate as observed by ^{1}H NMR.



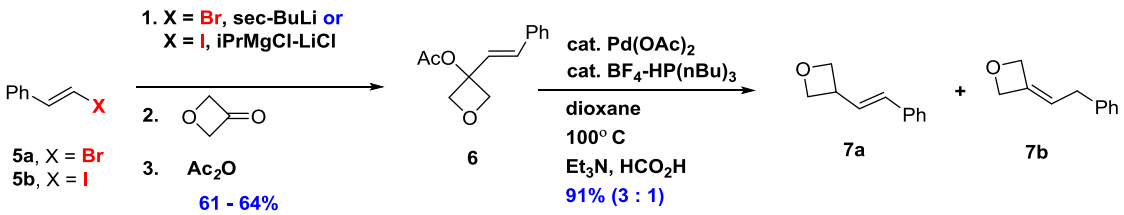
Scheme 1. Unsuccessful one carbon homologation of oxetane-3-one.

conditions required for oxetane ring closure[23] from 1,3-diol precursors are not suitable for 3-H/3-carbonyl containing oxetanes. Here, we report an alternative approach to install a carbonyl group off the 3-position of the oxetane through an unusual homologation sequence.

2. Results and discussion

Building from a strategy of avoiding oxetane ring formation, oxetane-3-one was anticipated to be a key starting material, commercially available in kilogram quantities. Homologation of this readily available ketone was the central challenge we faced. A large number of methods have been published on homologation of ketones to carbonyl compounds.[24] Our initial foray sought to use a classical homologation strategy of vinyl ether formation followed by hydrolysis to the aldehyde. Synthesis of **3** using an interrupted Ohira–Bestmann reaction[25] proceeded smoothly to provide the vinyl ether in 86% yield as a distillable liquid. Mild Brønsted and Lewis acids were then screened in an attempt to hydrolyze the enol ether. Hydrolysis reactions were monitored by running the reactions in deuterated solvents while monitoring by ^{1}H NMR. The only acid found to perform marginally as desired was trichloroacetic acid in a 1:1 mixture of CH_3CN/water (Scheme 1). All other acids either gave no reaction or led to complete ring opening to

Several other homologation strategies were attempted without success including furylation followed by furan cleavage by ozonolysis or treatment with Oxone,[26] hydrolysis of the α-cyanoepoxide, and hydrolysis of a ketene acetal. Then, we investigated a strategy based on regioselective Pd-catalyzed reductive cleavage of an allylic acetate.[27–29] Previous work had established the ability for regiocontrol in hydride addition to either side of a palladium-allyl species depending on the selected conditions. The more hindered side of the Pd-allyl intermediate is preferentially reduced when P(nBu)$_3$ is used as the ligand and trimethylamine/formic acid is used as the hydride source. With this knowledge in hand, we prepared allylic acetate **6** using two related procedures (Scheme 2). 1,2-addition of either (*E*)-styryllithium or the corresponding Grignard reagent to oxetane-3-one followed by quenching the alkoxide with acetic anhydride afforded **6** in 61–64% yield on a 0.5 mol scale without chromatography.



Scheme 2. Synthesis of *trans*-stryl oxetane, **7a**.

Pd-catalyzed reductive cleavage of allylic acetate **6** was accomplished under modified conditions to those reported by Tsuji, Meijere and Salaun.[28] The reaction required heating at 100 °C for initiation and short reaction time (40–50 min) to avoid over reduction to the alkane. Pd(OAc)$_2$ was found to give the same yield as Pd(dba)$_2$ and produced fewer colored impurities. A further improvement was to use the air stable tri-n-butylphosphonium tetrafluoroborate[30] to generate the free phosphine ligand in-situ using

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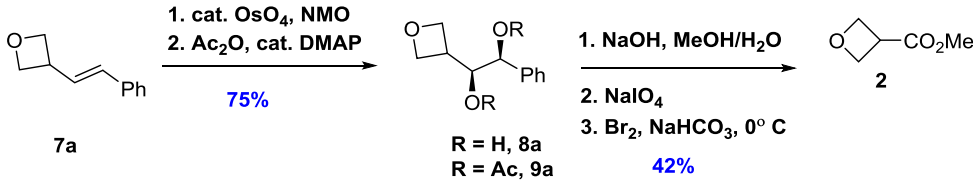
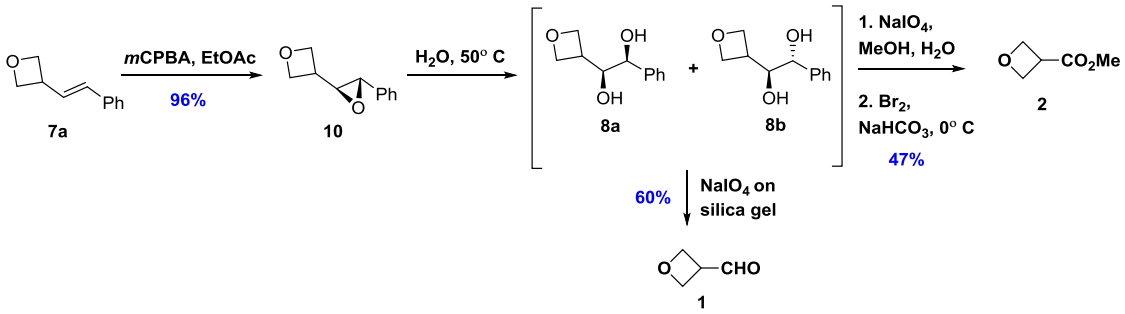
Et_3N, already present to form the formic acid salt. A 91% yield of **7a** and **7b** (3:1) formed under these conditions. Efforts to further improve the regioselectivity in favor of **7a** were not examined. Instead, we sought to demonstrate the feasibility of the final steps, first. Consequently, the **7a**+**7b** mixture was taken on to the epoxidation step, vide infra, and separation was more easily accomplished at intermediate **10** (Scheme 4). Alternatively, we separated the isomers by flash chromatography to afford **7a** as a single *trans* isomer.



Scheme 3. Oxadative cleavage of **7a**.



Scheme 4. Osmium-free oxidative cleavage of **7a**.

Ozonolysis of **7a** resulted in formation of benzaldehyde but without a trace of oxetane-3-carboxaldehyde (**1**) in the ^{1}H NMR of the crude reaction mixture. It is believed that **1** is not stable under ozonolysis, even at −78 °C. Interestingly, ozonolysis under flow conditions have shown utility for conversion of 3-furanyl oxetanes to the corresponding acids but only in 3,3-disubstituted cases.[31] However, we did not attempt ozonolysis under flow conditions. Instead, we turned our attention to a stepwise oxidation process via the 1,2-diol intermediate. Oxidative cleavage of **7a** using the 2,6-lutidine modification of the Lemieux–Johnson protocol[32] failed to form clean **1**, although some benzaldehyde was observed in the complex mixture. We then used the Upjohn procedure (cat. OsO_4, NMO, EtOAc) to form *syn*-diol **8a**. Extractive removal of the product from *N*-methyl morpholine was impossible since **8a** was highly water soluble. As a result, diacetate **9a** was formed directly by adding excess Ac_2O/cat. DMAP to the dihydroxylation mixture. This procedure temporarily side-stepped the water solubility issue associated with **8a**. The diacetate was extracted and purified to afford a 75% yield of **9a**. This temporary detour provided a convenient intermediate used to test the oxidative cleavage step via in situ hydrolysis back to **8a** prior to cleavage.

A mild method for one-pot conversion of a 1,2-diol to the cleaved methyl esters was published by Lichtenthaler in 1988.[33] This two-step one pot oxidation using $NaIO_4$ in aqueous methanol followed by aldehyde to ester oxidation using bromine or iodine under mildly basic conditions is a simple, practical procedure likely underutilized by chemists outside of the carbohydrate arena. Because of the sensitivity of the oxetane, this method appeared ideal for synthesis of ester **2**. Therefore, diacetate **9a** was hydrolyzed back to diol **8a** (NaOH, aq EtOH), treated with $NaIO_4$ at room temperature and then oxidized to the methyl ester using Br_2, $NaHCO_3$ at 0 °C to complete a three-step one pot synthesis of **2** in 42% yield.

While the sequence described in Scheme 3 provided small quantities of **2**, for larger scale work, we sought an osmium-free dihydroxylation procedure and wished to avoid the unnecessary diacetate formation. To achieve these goals, we converted **7a** to epoxide **10** in 96% yield using mCPBA in EtOAc. Aqueous hydrolysis of the epoxide at 50 °C in water[34,35] provided a 1.5:1 mixture of *syn*:*anti* diols (**8a** and **8b**). This ratio was based on forming acetates **9a** and **9b** and comparing the ^{1}H NMR of the mixture back to **9a** obtained via the osmium dihydroxylation reaction. The water soluble diol mixture was not isolated but taken on to the next step by adding methanol and $NaIO_4$ to the reaction mixture. Oxidative cleavage led to a mixture of benzaldehyde and the methyl acetal of oxetane-3-carboxyaldehyde. This mixture was then treated at 0 °C with $NaHCO_3$ and Br_2 to complete the oxidation to the esters. Since **2** is highly soluble in aqueous MeOH, the methyl benzoate by-product is removed by washing into heptane. Extraction into EtOAc and silica gel plug filtration afforded **2** in 47% from **10**.

For synthesis of aldehyde **1**, the Lichtenthaler oxidation step described above is skipped. To avoid hydrate formation, non-aqueous conditions are used for the oxidative cleavage. Silica-gel supported $NaIO_4$ in DCM served as an ideal heterogeneous reagent for this purpose.[36,37] Treatment of epoxide **10** with warm water to form diols **8a** and **8b**, as before, was followed by removal of the water in vacuo. The diol mixture was dissolved in DCM and treated with $NaIO_4$ on silica-gel. After complete oxidative cleavage, the DCM was evaporated and the silica-gel was washed with heptane to remove benzaldehyde. Aldehyde **1** adheres to silica gel strongly and was washed off the silica gel using acetone. The aldehyde was isolated in 60% yield after silica gel filtration, taking care to remove the DCM without evaporation of the volatile product in the process.

3. Conclusion

In summary, synthesis of oxetane-3carboxaldehyde (**1**) and methyl oxetane-3-carboxylate (**2**) was accomplished via mild

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homologation of oxetane-3-one. Classical homologation approaches were unsuccessful in our hands due to the sensitivity of oxetane ring. Consequently, a styrene-based homologation sequence was developed. The homologation involved regioselective deacetylation to form **7a** followed by stepwise oxidation. The final epoxide hydrolysis and oxidation steps were telescoped into convenient one pot procedures. In this way, epoxide **10** serves as a convenient precursor to either **1** or **2** by choosing the appropriate oxidative cleavage conditions. Synthesis of methyl ester **2** involved a two-step, one pot oxidation using $NaIO_4$ in aqueous methanol followed by treatment with $Br_2/NaHCO_3$. For aldehyde **1**, the use of silica-gel supported $NaIO_4$ avoided formation of the water soluble hydrate. Both oxidation procedures took advantage of the high polarity of the oxetane to conduct a liquid–liquid separation from the non-polar benzene containing by-products. Further optimization of these procedures could lead to an improved process capable of delivery of bulk quantities of these important heterocycles.

4. Experimental section

4.1. General remarks

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Removal of solvent under reduced pressure or concentration refers to distillation using Büchi rotary evaporator attached to a vacuum pump (3 mm Hg). Products obtained as solids or high boiling oils were dried under vacuum (1 mm Hg). Silica gel chromatography was performed either by CombiFlash (ISCO), SP4 or Isolera (Biotage) purification systems. All reactions were performed under a positive pressure of nitrogen, argon, or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, unless otherwise indicated. Analytical thin-layer chromatography was performed on glass-backed Silica Gel 60_F 254 plates (Analtech, 0.25 mm) and eluted with the appropriate solvent ratios (v/v). The reactions were assayed by high performance liquid chromatography-mass spectrometry (LC-MS) or thin-layer chromatography (TLC) and terminated as judged by the consumption of starting material. The TLC plates were visualized by UV, *p*-anisaldehyde, phosphomolybdic acid, or iodine staining. Microwave assisted reactions were run in a Biotage Initiator. ^{1}H NMR spectra were recorded on a Bruker XWIN-NMR (400 MHz) spectrometer. Proton resonances are reported in parts per million (ppm) downfield from tetramethylsilane (TMS). ^{1}H NMR data are reported as multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintuplet; sept, septuplet; dd, doublet of doublets; dt, doublet of triplets; bs, broad singlet). For spectra obtained in $CDCl_3$, DMSO-d_6, and CD_3OD, the residual protons (7.27, 2.50, and 3.31 ppm, respectively) were used as the internal reference. The progress of reactions and the purity of products were measured using the LCMS at 254 and 220 nm wavelengths and either electrospray ionization (ESI) positive mode or atmospheric-pressure chemical ionization (APCI) in positive mode. Combustion analysis was performed by Atlantic Microlab, Inc. Norcross, GA. Compound **5a** was purchased from Combi-Blocks as a 6:1 *trans* to *cis* mixture of isomers and was distilled under reduced pressure using a 3-foot Vigreux column to enrich to a 10:1 *trans* to *cis* mixture prior to use. Compound **5b** (99% *trans*) was prepared following a literature procedure.[38]

4.2. Procedures

*4.2.1. 3-(Methoxymethylene)oxetane (**3**).* A 50 mL round bottom flask containing MeOH (100 mL) was charged with ethyl 2-diazo-2-(dimethoxyphosphoryl)acetate (5.00 g, 26.0 mmol) and oxetane-3-one (2.81 g, 39.0 mmol). After cooling to 0 °C, K_2CO_3 (7.20 g, 52.1 mmol) was added in one portion. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction mixture was partitioned between Et_2O (200 mL) and water (200 mL). The organic phase was separated and the aqueous phase was extracted with ether (1×200 mL).

The combined organic phases were dried over sodium sulfate, concentrated to dryness, and purified using a short silica gel column (120 g) and eluting with a gradient of 0–40% EtOAc in pentane. After concentration of the fractions using a water bath temperature below 20 °C, the title compound was obtained as a colorless oil (2.25 g, 86% yield). **^{1}H NMR (400 MHz, $CDCl_3$)** δ ppm 5.81 (quin, *J*=2.2 Hz, 1 H), 5.31 (q, *J*=2.5 Hz, 2 H), 5.19 (q, *J*=2.4 Hz, 2 H), 3.56 (s, 3 H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ ppm 137.01, 10.5, 76.5, 58.7.

*4.2.2. (E)-3-Styryloxetan-3-yl acetate (**6**).* (a) Starting with **5a**, (*E*)-beta-bromostyrene. A 5 L 3-neck flask was equipped with N_2 inlet, large ice bath, addition funnel and overhead stirrer was charged with **5a** (108 g, 588 mmol, 10: 1 *trans* to *cis* ratio). 1.1 L of MTBE was added and the reaction was cooled to −70 °C. sec-BuLi (800 mL of 1.4 M in cyclohexane, 1120 mmol) was added dropwise over 60 min. The reaction was allowed to stir for 10 min at −70 °C and checked by LCMS to ensure complete Li–Br exchange. The reaction was complete as judged by the LCMS showed only styrene at this stage and no bromide remaining. Oxetane-3-one (40.4 g, 560 mmol) was then added as a solution in MTBE (200 mL) dropwise over 45 min while maintaining the temperature at −70 °C. After stirring for 1 h longer, LCMS analysis showed that the reaction was complex. Ac_2O (180 mL, 1900 mmol) was added dropwise and the mixture became a thick white slurry. The reaction was allowed to warm to rt overnight for convenience. The reaction was quenched with water (200 mL) and the layers separated. The aq layer was extracted once with MTBE (800 mL) and the combined organic extract washed with satd aq NaCl (×1) and dried over MgSO4. The MTBE was removed in vacuo and the AcOH removed by adding toluene (70 mL) and concentrating again. The resulting oil was placed under reduced pressure (high vac) for 1 h when crystals began to grow. The crude material was recrystallized from tBuOH (100 mL). After allowing the amber tBuOH solution to sit overnight at room temperature, white crystals formed. These were collected to afford 60 g of 99% pure material by ^{1}H NMR. The filtrate was concentrated and a second crop (7 g) of crystals were obtained. The filtrate was concentrated again and a third crop (7 g) of crystals obtained for a total yield of 74 g (61%) as a 70: 1 mixture of *trans* to *cis* isomers. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38–7.45 (m, 2H), 7.34 (t, *J*=7.3 Hz, 2H), 7.23–7.30 (m, 1H), 6.70 (d, *J*=16.3 Hz, 1H), 6.58 (d, *J*=16.3 Hz, 1H), 4.92 (d, *J*=7.8 Hz, 2H), 4.82 (d, *J*=7.8 Hz, 2H), 2.15 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.3, 135.7, 130.9, 128.5, 128.1, 126.8, 126.6, 81.0, 78.8, 21.0. Anal. Calcd for C, 71.54; H, 6.47. Found: C, 71.42; H 6.49.

(b) Starting with **5b**, (*E*)-beta-iodostyrene. To a yellow solution of **5b** (18.0 g, 78.2 mmol) in dry THF (360 mL) was added i-PrMgCl-LiCl (72 mL of 1.3 M in THF, 94 mmol) dropwise at −15 °C. The resulting mixture was warmed to 0 °C and stirred for 40 min. To the mixture was added oxetane-3-one (6.7 g, 86 mmol) in dry THF (80 mL) and the mixture was stirred at 0 °C for 30 min. TLC (PE/EA=1/1) showed most of **5b** was consumed. Ac_2O (16.0 g, 156 mmol) was added at 0 °C and the mixture was warmed to room temperature. After stirring at for 30 min, solids formed and the mixture was stirred at room temperature for 16 h. The reaction was quenched by pouring into water (500 mL). Extraction with EtOAc (300 mL×2) was followed by washing with brine (300 mL). The organic extract was dried over Na_2SO_4 and concentrated in vacuo to afford 20 g of crude product as an oil. The crude material was purified by silica gel chromatography eluting with a gradient of 0–50% EtOAc in petroleum ether to afford **6** (11 g, 64%) as pale yellow solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38–7.45 (m, 2H), 7.34 (t, *J*=7.34 Hz,

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2H), 7.23–7.30 (m, 1H), 6.70 (d, *J*=16.3 Hz, 1H), 6.58 (d, *J*=16.3 Hz, 1H), 4.92 (d, *J*=7.8 Hz, 2H), 4.82 (d, *J*=7.8 Hz, 2H), 2.15 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 169.3, 135.7, 130.9, 128.5, 128.1, 126.8, 126.6, 81.0, 78.8, 21.0.

*4.2.3. (E)-3-Styryloxetane (**7a**).* A 1 L round bottom flask was charged with **6** (15 g, 69 mmol, 70:1 mixture of *trans* to *cis*) and dry 1,4-dioxane (300 mL). N_2 was bubbled through the solution for 10 min to deoxygenate the solvent. $Pd(OAc)_2$ (154 mg, 0.690 mmol) and $BF_4HP(nBu)_3$ (798 mg, 2.75 mmol) were added followed by Et_3N (31 mL, 240 mmol). After stirring at room temperature for 5 min, the flask was fitted with a reflux condenser and formic acid (9.1 mL, 240 mmol) was added. The reaction was heated to reflux with the oil bath temperature set at 110 °C. After 35 min, the reaction was checked by TLC (5% EtOAc in heptane) which showed the reaction to be complete. [NOTE: A short reaction time of 35–50 min is important to avoid over reduction.] The product spot elutes slightly higher than the starting material on TLC using 5% EtOAc in heptane. The reaction mixture was cooled to room temperature and poured into satd aqueous NaCl (80 mL) plus water (80 mL) and the organics extracted with EtOAc (×3). The combined organic layer was washed with satd aqueous NaCl (×2), dried over $MgSO_4$ and concentrated to a yellow oil. The oil was purified via flash chromatography eluting with a gradient of 1–20% EtOAc in heptane. Fractions containing **7a** and **7b** were collected and concentrated to afford 10 g (91%) as a 3: 1 mixture of isomers. **7a ^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.16–7.46 (m, 5H), 6.48–6.58 (m, 1H), 6.43 (d, *J*=15.9 Hz, 1H), 4.92 (dd, *J*=6.0, 8.1 Hz, 2H), 4.66 (t, *J*=6.4 Hz, 2H), 3.80–3.96 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.8, 131.2, 129.6, 128.6, 128.5, 127.5, 126.2, 77.2, 38.7. Anal. Calcd for C, 82.46; H, 7.55. Found: C, 82.61; H 7.68.

7b ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.35 (m, 2H), 7.21–7.26 (m, 1H), 7.16–7.21 (m, 2H), 5.35 (quint, *J*=2.3, 7.1 Hz, 1H), 5.20–5.25 (m, 2H), 5.17 (dd, *J*=1.2, 2.4 Hz, 2H), 3.22 (d, *J*=7.1 Hz, 2H).

*4.2.4. (1RS,2RS)-1-(Oxetan-3-yl)-2-phenylethane-1,2-diyl diacetate (**9a**).* **7a** (7.08 g, 44.2 mmol) was dissolved in EtOAc (110 mL). *N*-methylmorpholine-N-oxide (5.69 g, 48.6 mmol), deionized water (4.4 mL), and osmium tetroxide (11.0 mL of a 2.5 wt % solution in t-butanol, 0.88 mmol) were added. The solution was stirred at room temperature for 3 h as it darkened from yellow to orange. LCMS analysis showed most of the starting material had been consumed, and a new peak formed at the solvent front. To the reaction was added freshly-ground sodium thiosulfate (10.5 g, 66.3 mmol) and the reaction was stirred at room temperature for 40 min. The reaction was then cooled to 0 °C and Ac_2O (42 mL, 442 mmol) and DMAP (545 mg, 4.46 mmol) were added. The reaction was allowed to gradually warm to room temperature as the ice in the cooling bath melted and was stirred for 19 h at room temperature. Water (125 mL) was added and the aqueous layer was extracted with EtOAc (3×150 mL). The combined organic layers were washed with satd aq NaCl (100 mL), dried over magnesium sulfate, filtered, and concentrated to 13 g as a brown oil. Purification of this oil was accomplished on a 220 g silica column, eluting with 0–50% EtOAc in heptane. Obtained 9.2 g (75%) of **9a** (R_f=0.33 in 50% EtOAc/hept) as a colorless liquid which crystallized on standing to a white solid. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.28–7.40 (m, 5H), 5.72 (d, *J*=6.7 Hz, 1H), 5.55 (t, *J*=6.7 Hz, 1H), 4.62 (t, *J*=6.7 Hz, 1H), 4.56 (dd, *J*=6.0, 8.2 Hz, 1H), 4.34 (dd, *J*=6.5, 8.4 Hz, 1H), 4.14 (t, *J*=6.8 Hz, 1H), 3.15–3.28 (m, 1H), 2.09 (s, 3H), 2.08 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 170.2, 169.5, 135.9, 128.7, 128.6, 126.8, 75.4, 74.2, 72.7, 72.6, 35.8, 20.8, 20.6. Anal. Calcd for C, 64.74; H, 6.52. Found: C, 64.56; H 6.56.

*4.2.5. (1RS,2RS)-1-(Oxetan-3-yl)-2-phenylethane-1,2-diol (**8a**).* Diacetate **9a** (2.4 g, 8.6 mmol) was placed in a 250 mL round bottom flask and was dissolved in EtOH (10 mL). Water (20 mL) was added, followed by NaOH (760 mg, 19 mmol). The solution was heated at 70 °C for 60 min and a 0.25 mL aliquot was removed and concentrated to dryness. Complete hydrolysis was observed by checking the ^{1}H NMR of this water soluble intermediate. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.23–7.40 (m, 5H), 4.62–4.73 (m, 2H), 4.33 (d, *J*=6.97 Hz, 1H), 4.26 (dd, *J*=6.4, 8.1 Hz, 1H), 3.98 (q, *J*=8.0 Hz, 2H), 2.98–3.12 (m, 1H).

*4.2.6. 3-((2RS,3RS)-3-Phenyloxiran-2-yl)oxetane (**10**).* **7a** (6.5 g, 40 mmol) was dissolved in EtOAc (130 mL) and the mixture was cooled to 0 °C. *m*CPBA (21 g of 80%, 97 mmol) was added and the reaction was allowed to warm to room temperature and stir for 16 h. The reaction was judged complete by TLC (20% EtOAc in heptane) based on consumption of the starting material and formation of a new, weakly UV active spot formed at lower R_f (0.4 in 20% EtOAc in heptane), staining pink with PAA. The reaction was diluted with EtOAc and the organic layer was washed with saturated aqueous Na_2SO_3 (×2), satd aqueous $NaHCO_3$ (×3) and satd aq NaCl (×1). After drying over $MgSO_4$, the solvent was removed and the product purified via flash chromatography eluting with a gradient of 5–40% EtOAc in heptane. Fractions containing the product were pooled and concentrated to afford 7.0 g (96%) of **10** as a colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.26–7.41 (m, 5H), 4.84 (dt, *J*=6.3, 7.9 Hz, 2H), 4.59–4.69 (m, 2H), 3.68 (d, *J*=2.0 Hz, 1H), 3.30–3.35 (m, 1H), 3.21–3.30 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 136.6, 128.4, 128.2, 125.5, 73.0, 72.8, 62.3, 56.8, 36.3, 62.3, 56.8, 36.3; HRMS (ESI) calcd for $[M+H, C_{11}H_{12}O_2]^+$: 176.0837; found: 176.0839.

*4.2.7. Methyl oxetane-3-carboxylate (**2**).* Epoxide **10** (1.0 g, 5.67 mmol) was suspended in H_2O (20 mL), stirred and heated at 50 °C for 2 h [NOTE: An aliquot was removed, concentrated to dryness and the diol mixture treated with excess Ac_2O and catalytic DMAP. ^{1}H NMR analysis of the diacetate mixture showed a 1.5: 1 mixture of **9a** to **9b**.] To the aqueous diol solution, after cooling to room temperature, was added MeOH (10 mL). After further cooling to 0 °C a solution of $NaIO_4$ (1.9 g, 9.1 mmol) dissolved in warm water (20 mL) was added dropwise over 5 min. After 5 min at 0 °C, the ice bath was removed and the reaction was warmed and stirred at room temperature for 3 h ^{1}H NMR analysis of a 0.25 mL aliquot of the reaction mixture (extraction into $CDCl_3$) showed the oxidative cleavage reaction to be complete forming benzaldehyde and the oxetane aldehyde as a mixture of hydrate and aldehyde forms. $NaHCO_3$ (1.8 g, 21 mmol) was added. The reaction was cooled to 0 °C and Br_2 (1.4 g, 8.5 mmol) was added dropwise as a solution in MeOH (10 mL). The reaction was stirred at 0 °C for 1 h and at room temperature for 2 h. The excess Br_2 was quenched by pouring the reaction into an ice cold solution of Na_2SO_3 (3.5 g in 50 mL of ice water). The mixture was transferred to a separatory funnel and washed with heptane (×3) to remove methylbenzoate and remaining benzaldehyde. Then, the aqueous mixture was extracted with EtOAc (×4). The combined extract was washed with satd aq NaCl (×2) and dried over $MgSO_4$. After careful removal of the EtOAc at a water bath temperature of 10–15 °C, purification was accomplished using a 10 g silica plug (Varian–pre-packed) by loading the oil on the column using DCM, eluting with 3 column volumes of heptane followed by 4 column volumes of EtOAc. The fractions containing **2** (TLC 50% EtOAc in heptane/observing **2** using an I_2 chamber, 10 min). After removing the solvent, 313 mg (47%) of **2** was obtained as a colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 4.78–4.90 (m, 4H), 3.86 (tt, *J*=6.9, 8.5 Hz, 1H), 3.76 (s, 3H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 172.1, 72.5, 51.5, 38.0. Anal. Calcd for C, 51.72; H, 6.94. Found: C, 52.70; H 6.91.

*4.2.8. Oxetane-3-carboxaldehyde (**1**).* Epoxide **10** (4.4 g, 25 mmol) was added to water (50 mL) in a 100 mL round bottom flask while

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stirring. The oily suspension was heated at 50 °C for 2 h. The H_2O was removed in vacuo and the remaining colorless oil was dissolved in DCM (240 mL). Silica supported $NaIO_4$ (64 g of Aldrich 10% $NaIO_4$ by weight, 30 mmol) was added and the reaction was allowed to stir at room temperature for 16 h. The DCM was removed *in vacuo* using a water bath temperature between 10–15 °C. The resulting dry silica gel was suspended in heptane and washed with heptane (3×100 mL) in a sintered glass filter funnel, stirring well after each addition of heptane. The heptane washes were discarded. Then, the silica was washed with acetone (4×75 mL). The combined acetone washes were concentrated in vacuo using a water bath temperature between 10–15 °C. The oily residue plus white solid that formed was dry loaded onto a silica cartridge (Isco). The cartridge was placed on top of a 24 g Isco column and heptane (5 column volumes) eluted followed by DCM (25 column volumes). The DCM fractions were analyzed by TLC (100% DCM, R_f=0.1), staining with 2,4-DNP to visualize the aldehyde. Fractions containing the aldehyde were combined and concentrated to afford 1.3 g (60%) as a colorless oil. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 9.96 (d, J=2.5 Hz, 1H), 4.91–4.86 (m, 2H), 4.86–4.83 (m, 2H), 3.92–3.72 (m, 1H). **^{13}C NMR (101 MHz, $CDCl_3$)** δ 199.0, 70.3, 45.3.

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