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The strategic marriage of method and motif. Total synthesis of varitriol

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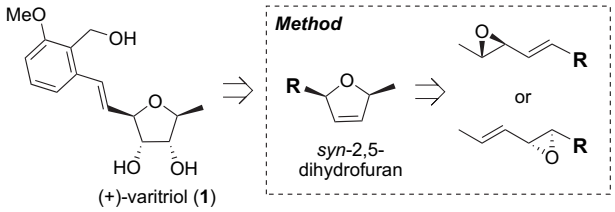
ABSTRACT

Detailed in this report are several new efficient synthetic approaches toward the natural product *anti* cancer agent varitriol, culminating in a concise total synthesis. A common theme for these routes is that they employ a new catalytic stereoselective vinyl oxirane ring expansion reaction, which provides rapid access to the common *cis*-2,5-tetrahydrofuran core. The combination of careful synthetic design and proper selection of starting materials results in an excellent marriage between this new method (vinyl oxirane ring expansion) and the motif (varitriol).

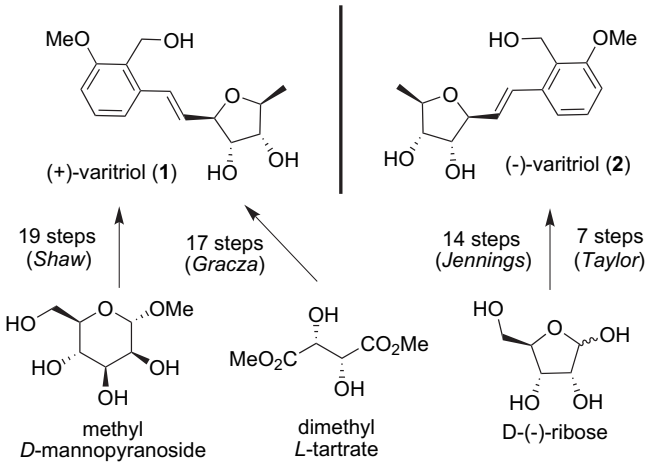
1. Introduction

The marine natural product varitriol (**1**, Scheme 1) was recently isolated and characterized.[1] Screening efforts of varitriol against the National Cancer Institute 60-cell line in vitro panel revealed promising activity against a number of important types of cancer. This encouraging *anti*-cancer activity, coupled with varitriol's heavily substituted tetrahydrofuran core, constitutes an ideal opportunity to showcase the strengths of our new copper-catalyzed vinyl oxirane ring expansion reaction (the 'method'),[2] which we have recently demonstrated can proceed in a stereoselective fashion.[3] In other words, we propose that our method is especially well suited for expediently assembling varitriol (the 'motif'). Of course, this success depends on the judicious choice of substituents (R=?), source material and well matched accompanying reactions. The studies presented herein are aimed at identifying the most suitable vinyl oxirane substrates for accessing varitriol.



Scheme 1. Motif (varitriol) and method (vinyl oxirane ring expansion).

Not surprisingly, given varitriol's attractive biological profile it has attracted the attention of synthetic chemists. Four syntheses of varitriol (**1**)[4] and its enantiomer (**2**)[5] have been completed to date (Scheme 2).[6,7] Interestingly, all these approaches have utilized chiral pool source materials. With the exception of Taylor's synthesis of **2**, the longest linear sequences seem rather long for a molecule like varitriol.[8] Our approach focuses on the rapid synthesis of the dihydrofuran core from non-chiral pool starting



Scheme 2. Chiral pool total syntheses of (+)- and (−)-varitriol.

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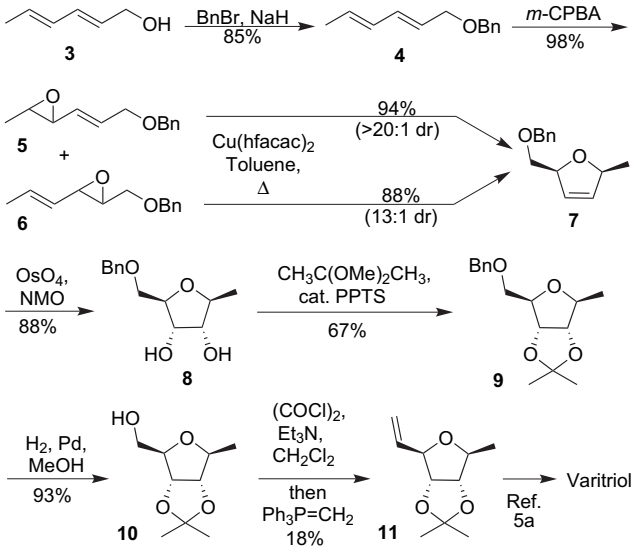
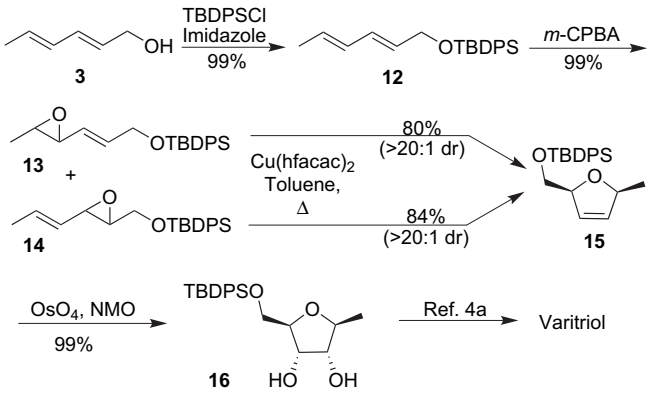
materials[9] with minimal use of protecting groups[10] and redox adjustments.[11]

Our synthetic efforts commenced with epoxidation of benzyl protected dienyl alcohol **4** (Scheme 3). The two vinyl oxirane constitutional isomers (**5** and **6**) were separated and subjected to the copper-catalyzed rearrangement conditions. Using $Cu(hfacac)_2$, both vinyl oxiranes rearranged to form the expected *cis*-2,5-dihydrofuran **7** in excellent yield and with high stereoselectivity.[3] Substrate controlled dihydroxylation (**8**) installed the natural product's other two stereocenters. At this point in the synthesis, the *cis*-diol was protected as an acetonide (**9**) and the benzyl protecting group of the primary alcohol removed by hydrogenolysis. Oxidation of the free alcohol (**10**) afforded an aldehyde, which was immediately subjected to a Wittig olefination reaction (**11**). Tetrahydrofuran product **11** is a known synthetic intermediate in a recently completed synthesis of varitriol by Jennings and co-workers.[5a] This new synthetic approach, allowed us to access **11** in eight steps from dienol **3**, which is four steps shorter than the earlier route from D-ribose. It is important to note, in comparing the two sequences, that our new route has not been executed using chiral starting materials. Literature examples support the notion that our new synthetic sequence lends itself well to established asymmetric epoxidation protocols. For example, Somfai[12] has demonstrated that **4** can be oxidized to (2*R*,3*R*)-**5** in good yield and 95% ee using one of Yian Shi's chiral diooxirane reagents. Advancing this product would provide access to (−)-varitriol (**2**). Interestingly, Shi has demonstrated that when TBS-protected **3** is oxidized, a mixture of (2*R*,3*R*)- and (4*R*,5*R*)- epoxides are produced, with the latter being a perfect match with our method to access (+)-varitriol (**1**).[13]



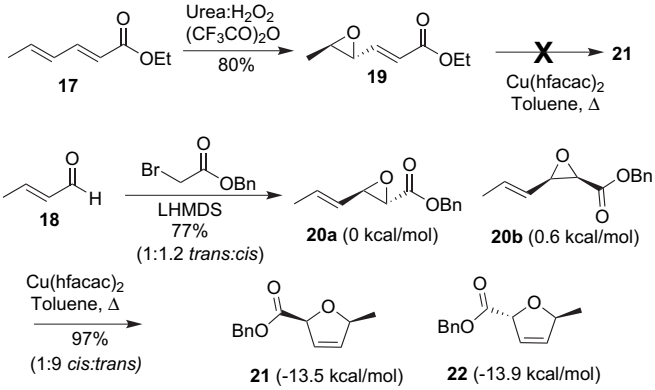
Scheme 3. Formal synthesis of varitriol (first approach).

In Shaw and co-workers total synthesis of natural (+)-varitriol (**1**),[4a] protected triol **16** (Scheme 4) served as a key intermediate. Our stereoselective vinyl oxirane ring expansion strategy seemed like a perfect fit for expediently accessing **16** and to further evaluate the functional group compatibility of our methodology. Furthermore, there seemed to be a need for a better diol protecting group as the aldehyde obtained from **10** performed very poorly in the Wittig reaction.[4a,5a] Shaw demonstrated in his synthesis that this issue could be addressed by using PMB-protecting groups instead of an acetonide to mask the diol. Our synthetic route commenced with silyl protection of dienol **3**. The resulting diene was epoxidized to furnish vinyl oxiranes **13** and **14**, which were readily separable. Both oxiranes ring expanded efficiently in the presence of $Cu(hfacac)_2$ to produce *cis*-2,5-dihydrofuran **15** in excellent yield and better than 20:1 stereoselectivity.[14] This result also establishes silyl group compatibility with our ring expansion conditions. Substrate controlled dihydroxylation using osmium tetroxide afforded **16** in only four steps from dienol **3**, which compares very favorably to Shaw's twelve step synthesis of **16** from methyl D-mannopyranoside.



Scheme 4. Formal synthesis of varitriol (second approach).

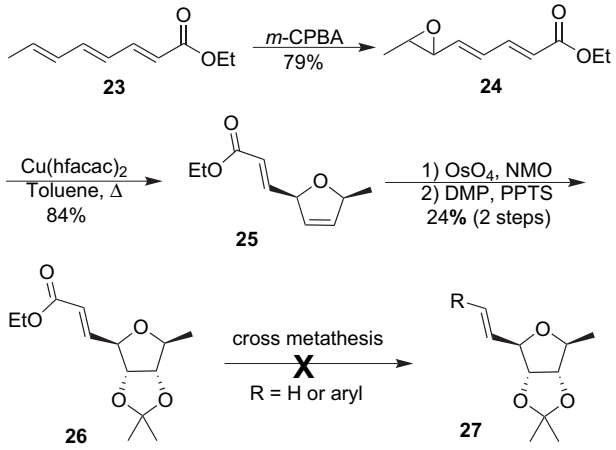
Although our new routes to these known synthetic intermediates are shorter than previous ones, they are not without room for improvements. In particular, there should be a way to bypass using a protecting group on the primary alcohol and thus truncate these routes by two more steps. Constitutional vinyl oxirane isomers **19** and **20** (Scheme 5), which can be accessed in a single step from **17**[15] and **18**,[16] respectively, seemed to fit this goal perfectly. Moreover, the significant steric and electronic differences between **19** and **20** might provide us with further mechanistic insights. Interestingly, vinyl oxirane **19** decomposed instead of ring expanding to the expected 2,5-dihydrofuran product **21**, while its constitutional isomers (**20**)[17] ring expanded nicely in high yield. From a mechanistic perspective, this result is interesting. If coordination of the copper catalyst is invoked for the mechanism of this reaction, then this result is not too surprising as the acrylate olefin moiety of **19** would be far poorer olefin donor than the olefin of **20**.[18] Upon further analysis, we learned that under the reaction conditions the *cis*-isomer (**21**) had epimerized to the thermodynamically more stable *trans*-isomer (**22**).[19] Although, the epimerization of **21** to **22** precluded advancement of this product,[20] this new route succeeded in avoiding the use of protecting groups to access a functionalized dihydrofuran product.



Scheme 5. Third synthetic approach toward varitriol.

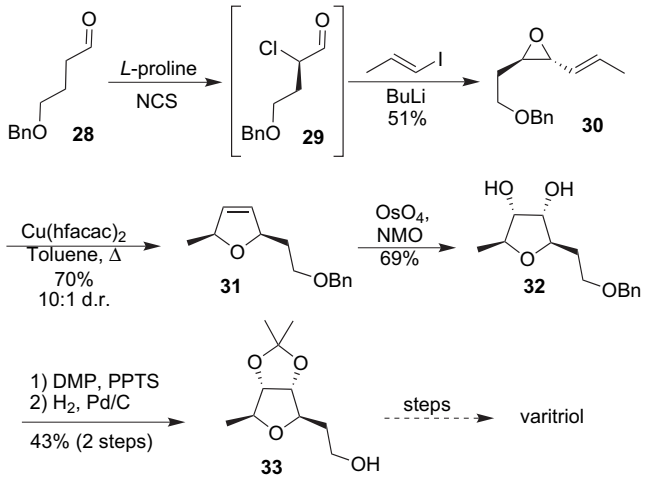
Is there room for further improvements? Although this last route is potentially very short, the union of the furan moiety and

the aryl group would require a three step sequence of ester reduction, Wittig olefination followed by cross metathesis. The simplest way to shave off one more step from this sequence would be to use a Wittig or Julia olefination instead of the cross metathesis reaction to join the two fragments. Alternatively, by using a substrate such as **23** (Scheme 6) that contains the desired exocyclic carbon atoms there was a possibility of saving three steps and providing access to varitriol in only four steps. Toward that end, commercially available triene **23** was selectively transformed to vinyl oxirane **24**, which upon treatment with $Cu(hfacac)_2$ ring expanded efficiently to the expected *cis*-2,5-dihydrofuran product **25**. Dihydroxylation of diene **25** affords a mixture of products that when protected yields acetonide **26**. This product is only a cross metathesis away from varitriol. At the outset, it was well understood that acrylate **26** was a poorly matched cross metathesis substrate.[21] Therefore it was not entirely surprising that we were unable to convert **26** to **27** using either ethylene or styrene derivatives. Determined to advance this highly desirable substrate, we also evaluated relay metathesis substrates[22] wherein the ethyl ester had been replaced with an appropriate allyl ester group but to no avail.



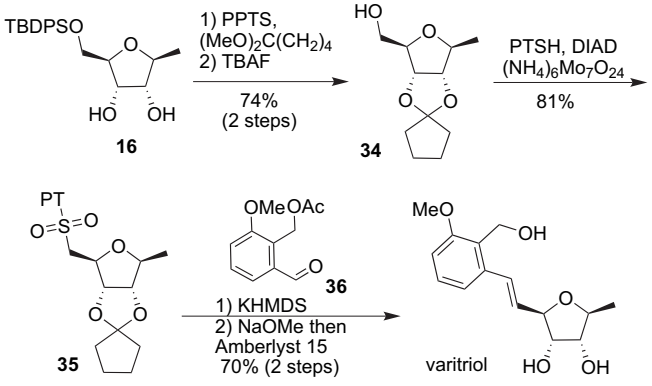
Scheme 6. Fourth synthetic approach toward varitriol.

Inspired by how convergently components were brought together by using the Darzen's reaction (Scheme 5) and coupled with our desire to access enantiopure vinyl oxirane starting materials, we decided to explore an alternative approach (Scheme 7). We argued that addition of an appropriate vinyl nucleophile to a chiral α-chloro aldehyde would expediently afford the desired chiral vinyl oxirane substrate. Toward that end, commercially available aldehyde **28** was chlorinated using Jorgensen's organocatalytic procedure[23] and then subjected crude to the addition of vinyl lithium reagent[24] to afford vinyl oxirane **30**. Ring expansion of this vinyl oxirane provided *cis*-2,5-dihydrofuran product **31**, which was then dihydroxylated (**32**). The diol was protected as an acetonide and the benzyl ether was deprotected using palladium mediated hydrogenolysis to furnish **33** in only six steps from aldehyde **28**. Alcohol **33** is a versatile synthetic intermediate that could be dehydrated to afford cross metathesis substrate **11** (Scheme 3) without relying on the challenging olefination step. Alternatively, **33** could be oxidized to an aldehyde and then reacted with the appropriate aryl anion. The resulting secondary alcohol would then be dehydrated to afford varitriol. Although in the end **33** was not chosen to be advanced to the natural product, the synthetic sequence in Scheme 7 serves as a reminder that dienes are not necessarily the best way to access vinyl oxiranes. This new approach offers access to enantiopure material, via **29**, while at the same time ensuring access to a single vinyl oxirane product. While in contrast 1,3-dienes are a challenging substrate class when it comes to asymmetrically accessing a single vinyl oxirane constitutional isomer product.



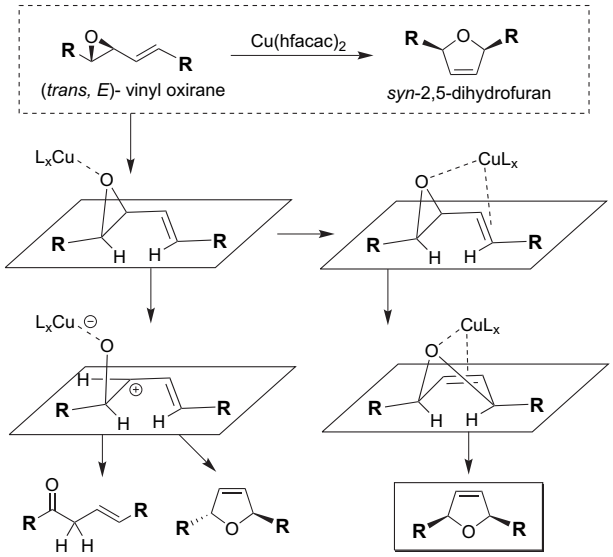
Scheme 7. Fifth synthetic approach toward varitriol.

In order to complete the synthesis of varitriol, we then decided to utilize readily available diol **16**. Protection of the diol in **16** as an acetal followed by treatment with tetrabutylammonium fluoride (TBAF) afforded **34**. A variety of sequences can be envisioned to convert primary alcohol **34** to varitriol, the most efficient of which is depicted in Scheme 8. This involves a Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH)[25] followed by in situ oxidation with ammonium molybdate tetrahydrate to give sulfone **35**. Julia olefination[26] with aldehyde **36** produced exclusively the *E*-olefin without any furan epimerization in high yield. The analogous Julia olefination with the sulfone and aldehyde moieties reversed was shown to be inferior due to poor yield and olefin selectivity. Deprotection of the olefination product afforded varitriol, which matched previously reported data.



Scheme 8. Total synthesis of varitriol.

What accounts for the excellent stereoselectivity of our copper-catalyzed vinyl oxirane ring expansion reaction? We currently favor a chelation model to account for the observed success in stereoselectively ring expanding vinyl oxiranes (Scheme 9). We have previously shown that *trans*- and *cis*-*E* vinyl oxiranes can be stereoselectively ring expanded to *cis*- and *trans*-2,5-dihydrofuran products, respectively.[3] Not surprisingly, and in accordance with our oxirane–olefin chelation model, the corresponding *Z*-olefins were shown to be poor substrates with the exception being cyclic vinyl oxiranes.



Scheme 9. Chelation model for stereoselective oxirane ring expansion.

In this chelation scheme, we envision initial coordination of the copper catalyst to the lone pairs of the oxygen atom followed by coordination to the olefin prior to ring expansion. The 2,5-dihydrofuran product forms a less effective chelate with the catalyst and is therefore quickly released to turnover the catalyst. The main competing pathway for this ring expansion is highly dependent on the steric and electronic nature of the vinyl oxirane being investigated. If ring expansion does not occur rapidly, an allylic cation can be formed that can either form the isomeric oxirane and then ring expand or alternatively undergo a 1,2-hydride shift.

In conclusion, we have explored the suitability of our new copper-catalyzed vinyl oxirane ring expansion reaction for the total synthesis of varitriol. In our opinion, this reaction is a good match for varitriol as is evident from our expedient approaches. To realize this goal, the important secondary challenge of this project became to design an optimal synthesis of the vinyl oxirane precursor and the most efficient sequence from the dihydrofuran product. This reminds us that in order to accomplish short and efficient syntheses, a good method needs the support of good synthetic design and insightful selection of starting materials. The message of these synthetic explorations toward varitriol, are clear. New synthetic methods provide new opportunities for synthetic design, which in turn enable better approaches to well matched targets. This means that there is a great need for developing useful new synthetic methods, especially asymmetric ones that can complement the use of chiral pool source materials.

2. Experimental section

2.1. General information

Commercial reagents were purchased and used without further purification. All glassware was flame dried and reactions were performed under a nitrogen atmosphere, unless otherwise stated. Toluene, benzene, dichloromethane, diethyl ether, and THF were dried over a column of alumina. Flash chromatography was done with Silicycle SiliaFlash® F60 silica, and thin layer chromatography (TLC) was performed with EMD 250 μm silica gel 60-F_{254} plates. ^{1}H and ^{13}C NMR data was acquired on a Varian Inova 400, 500, or 600 (400, 500 or 600 MHz) spectrometer and referenced to residual protic solvent. IR was taken on a Mattson Instruments Research Series FTIR spectrometer. High-resolution mass spectrometry was performed at the University of Illinois at Urbana-Champaign facility.

*2.1.1. Benzyl ether **4**.* A 1 L flask equipped with a stir bar containing DMF (500 mL) and sodium hydride (60% dispersion in mineral oil, 4.49 g, 112.24 mmol) was cooled to 0 °C in an ice bath, and then a solution of (2*E*, 4*E*)-2,4-hexadien-1-ol (**3**) (10.0 g, 102 mmol) in DMF (10 mL) was slowly added. After 1 h, sodium iodide (0.49 g, 20.5 mmol) and benzyl chloride (11.8 mL, 13.0 g, 102 mmol) were added. After 2 h, the reaction was quenched with water and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted (2×) with diethyl ether. The combined organic portions were then washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by chromatography to give benzyl ether **4** as a colorless oil (16.26 g, 85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.26 (m, 5H), 6.23 (dd, J=15.2, 10.5, 1H), 6.13–6.03 (m, 1H), 5.71–5.60 (m, 2H), 4.51 (s, 2H), 4.05 (d, J=6.3, 2H), 1.77 (d, J=6.7, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 133.6, 131.0 130.3, 128.6, 128.0, 127.8, 126.8, 72.1, 70.8, 18.3; IR (neat) 3062, 3026, 2932, 2910, 2853, 1496, 1453, 1361, 1113, 1073, 990 cm^{-1}; HRMS (EI$^+$) m/z 188.1198 [calculated mass for $C_{13}H_{16}O$ (M^+) 188.1201].

*2.1.2. Vinyl oxiranes **5** and **6**.* To a 500 mL flask equipped with a stir bar was added methylene chloride (300 mL), (*E*,*E*)-1-benzyloxy-2,4-hexadiene (5.9 g, 31.3 mmol), Na_2HPO_4 (7.73 g, equal mass with *m*-CPBA), and *m*-CPBA (77%, 7.73 g, 34.5 mmol). After 1 h, the reaction was cooled to 0 °C and filtered through Celite. It was then diluted with additional diethyl ether and washed with 1 M NaOH, a saturated $NaHCO_3$ solution (2×), water, and dried over $MgSO_4$. The solvent was removed in vacuo to give a clear oil (6.27 g, 98%) that was a 1.5:1 (**5**:**6**) mixture of regioisomers. The regioisomeric vinyl oxirane products could be separated by column chromatography (10–20% ether/90–80% pentane). For compound **5** characterization data matched previously reported in the literature.[27] (**6**) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.11 (m, 5H), 6.01–5.88 (m, 1H), 5.20 (dddd, J=15.3, 8.3, 3.1, 1.5, 1H), 4.67–4.49 (m, 2H), 3.74 (dd, J=11.5, 3.2, 1H), 3.51 (dd, J=11.5, 5.5, 1H), 3.24 (dd, J=8.3, 2.2, 1H), 3.13–3.07 (m, 1H), 1.74 (dd, J=6.6, 1.6, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 132.5, 128.6, 128.1, 128.0, 128.0, 73.5, 70.2, 58.8, 56.3, 18.1; IR (neat) 3087, 3063, 3029, 2989, 2966, 2938, 2917, 2857, 1496, 1453, 1364, 1239, 1206, 1105, 963, 874, 739, 699 cm^{-1}; HRMS (EI$^+$) m/z 204.11496 [calculated mass for $C_{13}H_{16}O_2$ (M^+) 204.11503].

*2.1.3. 2,5-Dihydrofuran **7** (obtained from **5**).* To a flame dried 13×100 mm threaded culture tube was added vinyl oxirane **5** (25 mg, 0.12 mmol) in dry toluene (1 mL). The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150 °C. A syringe pump was used to add toluene over 8 h (0.5 mL, 0.63 mol %/hour), which contained Cu(hfacac)$_2$ (3.0 mg, 0.0061 mmol, 0.05 equiv). The solution was heated for a total of 12 h and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with ethyl acetate and then purified by flash chromatography on silica gel (10% ether/90% pentane, $KMnO_4$) to yield of 2,5-dihydrofuran **7** (23.5 mg, 94%, 0.12 mmol), (Crude diastereomeric ratio >20:1, purified >20:1 *cis*/*trans*).

*2.1.4. 2,5-Dihydrofuran **7** (obtained from **6**).* To a flame dried 13×100 mm threaded culture tube was added vinyl oxirane **6** (25 mg, 0.12 mmol) in dry toluene (1 mL). The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150 °C. A syringe pump was used to add toluene over 8 h (0.5 mL, 0.63 mol %/hour), which contained Cu(hfacac)$_2$ (3.0 mg, 0.0061 mmol, 0.05 equiv). The solution was heated for a total of 12 h and then cooled to room temperature. The reaction mixture

was filtered through neutral alumina (activity grade 1) washing with ethyl acetate and then purified by flash chromatography on silica gel (10% ether/90% pentane, $KMnO_4$) to yield 2,5-dihydrofuran **7** (22.0 mg, 88%, 0.11 mmol), (Crude diastereomeric ratio 13:1, purified >20:1 *cis*/*trans*). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52–7.00 (m, 5H), 5.85 (d, J=6.0, 1H), 5.78 (d, J=6.0, 1H), 4.99–4.90 (m, 2H), 4.66–4.54 (m, 2H), 3.54–3.47 (m, 2H), 1.29 (d, J=6.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 133.1, 128.5, 127.8, 127.7, 127.1, 85.5, 82.5, 74.1, 73.6, 23.0; IR (neat) 3312, 3089, 3064, 3031, 2971, 2924, 2859, 1453, 1366, 1094 cm^{-1}; HRMS (EI$^+$) m/z 202.0996 [calculated mass for $C_{13}H_{14}O_2$ ($M-H_2^+$) 202.0994].

*2.1.5. Diol **8**.* To a stirred flask containing acetone (5.6 mL), water (5.6 mL), dihydrofuran **7** (1.00 g, 4.93 mmol), and 4-methylmorpholine *N*-oxide (1.01 g, 8.63 mmol) was added OsO_4 (2.5% in ^{t}BuOH, 0.25 mL). After 24 h, the reaction was quenched with a solution of sodium bisulfite and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3×). The combined organic portions were dried over Na_2SO_4. The solvent was removed in vacuo and was purified by chromatography (30–70% ethyl acetate/70–30% hexanes) to give diol **8** (1.03 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H), 4.56 (d, J=1.1, 2H), 3.96 (t, J=5.5, 1H), 3.91 (q, J=4.8, 1H), 3.81 (ap, J=6.2, 1H), 3.66 (ddd, J=14.4, 8.5, 4.6, 1H), 3.59 (dd, J=4.7, 0.9, 2H), 3.15 (br s, 1H), 3.04 (br s, 1H), 1.28 (d, J=6.3, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.1, 128.6, 127.9(7), 127.9(6), 82.8, 79.6, 76.4, 73.8, 72.8, 71.0, 19.0. IR (neat) 3388, 2906, 1496, 1452, 1094, 1019, 738, 696 cm^{-1}. HRMS (ESI) m/z 239.1275 [calculated mass for $C_{13}H_{19}O_4$ (M^+) 239.1283].

*2.1.6. Acetonide **9**.* To a 100 mL flask equipped with a stir bar was added methylene chloride (40 mL), diol **8** (1.03 g, 4.32 mmol), pyridinium *p*-toluenesulfonate (0.22 g, 0.86 mmol), and 2,2-dimethoxypropane (4.5 g, 43.2 mmol). The reaction was left to stir for 3 h. It was diluted with methylene chloride and washed with $NaHCO_3$ and brine. The solution was dried over Na_2SO_4 and purified by chromatography (10–30% ether/90–70% pentane) to give acetonide **9** (0.88 g, 67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40–7.26 (m, 5H), 4.59 (s, 2H), 4.55 (dd, J=6.96, 4.47, 1H), 4.25 (dd, J=6.94, 5.05, 1H), 4.06 (dd, J=9.55, 4.40, 1H), 4.03–3.91 (m, 1H), 3.64–3.52 (m, 2H), 1.53 (s, 3H), 1.33 (s, 3H), 1.31 (d, J=6.3, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 128.6, 128.0, 127.9, 114.9, 86.2, 83.2, 82.6, 80.9, 73.8, 70.7, 27.6, 25.7, 19.2; IR (neat) 3088, 3062, 3031, 2982, 2932, 2870, 1497, 1454, 1372, 1253, 1240, 1211, 1158, 1118, 1076 cm^{-1}; HRMS (EI$^+$) m/z 278.1515 [calculated mass for $C_{16}H_{22}O_4$ (M^+) 278.1518].

*2.1.7. Primary alcohol **10**.* To a 50 mL flask equipped with a stir bar was added methanol (25 mL), acetonide **9** (0.80 g, 2.87 mmol), and 10% Pd/C (0.029 g). A balloon of hydrogen gas was then added. After 18 h, the reaction was filtered through Celite with ethyl acetate. The solvent was removed in vacuo to afford primary alcohol **10** (0.50 g, 93%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.61 (dd, J=6.99, 4.51, 1H), 4.23 (dd, J=6.96, 5.23, 1H), 4.12–3.88 (m, 2H), 3.82 (ddd, J=11.93, 4.90, 3.37, 1H), 3.67 (ddd, J=12.00, 7.63, 4.45, 1H), 2.00 (dd, J=7.62, 5.03, 1H), 1.53 (s, 3H), 1.33 (s, 3H), 1.31 (d, J=6.35, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 115.0, 86.3, 84.3, 81.8, 80.7, 63.0, 27.6, 25.6, 19.1; IR (neat) 3466, 2982, 2934, 2878, 1456, 1382, 1263, 1241, 1212, 1158, 1122, 1076 cm^{-1}; HRMS (EI$^+$) m/z 189.1123 [calculated mass for $C_9H_{17}O_4$ ($M+H^+$) 189.1127].

*2.1.8. Vinyl tetrahydrofuran **11**.* Stock solutions of all reagents were prepared. To a 5 mL flask equipped with a stir bar was added CH_2Cl_2 (1 mL) and a solution of oxalyl chloride (0.0210 g, 0.166 mmol). The solution was cooled to −78 °C and DMSO was added (0.0259 g, 0.332 mmol). After 15 min, primary alcohol **10** (0.0260 g, 0.138 mmol) was added, and the reaction was left to stir for 40 min at −78 °C. After 40 min, triethyl amine was added (0.0699 g, 0.691 mmol), and after an additional 20 min, the reaction was warmed to 0 °C in an ice bath. After 30 min, the reaction was filtered through a plug of Celite with 50% diethyl ether/pentane. The solvent was removed in vacuo, 0.5 mL of diethyl ether was added, and the solution was cooled to 0 °C. In the meantime, methyl triphenylphosphonium bromide (0.247 g, 0.691 mmol) was added to a 10 mL flask containing diethyl ether (3.5 mL), cooled to 0 °C, and equipped with a stir bar. Potassium *tert*-butoxide (0.0814 g, 0.725 mmol) was added to the solution. After 1 h, 1.5 mL of this solution (2 equiv) was added to the crude aldehyde solution. Upon completion, the reaction was quenched with ammonium chloride and diluted with diethyl ether. The layers were separated, and the organic layer was washed with saturated NaCl and dried over $MgSO_4$. The solvent was removed in vacuo. The product was purified by chromatography (5% ethyl acetate/95% hexanes) to give vinyl tetrahydrofuran **11** (0.0047 g, 18%). The NMR data matched that previously published in the literature.[5a] ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.90 (ddd, J=17.08, 10.50, 6.43, 1H), 5.39 (td, J=17.23, 1.35, 1H), 5.23 (td, J=10.50, 1.28, 1H), 4.45 (dd, J=6.99, 4.95, 1H), 4.28 (ddd, J=17.44, 6.60, 4.89, 2H), 4.07–3.89 (m, 1H), 1.55 (s, 3H), 1.34 (s, 3H), 1.33 (d, J=6.41, 3H).

*2.1.9. Silyl ether **12**.* To a 250 mL flask was added 2,4-hexadien-1-ol (3.4 g, 34.6 mmol, 1 equiv) and CH_2Cl_2 (100 mL). A stir bar was added followed by imidazole (4.2 g, 61.7 mmol, 1.8 equiv). Lastly, *tert*-butylchlorodiphenylsilane (12.6 g, 45.8 mmol, 1.3 equiv) was added and the reaction was stirred for 10 h at room temperature. The reaction was diluted with diethyl ether and washed with 1 M HCl. The solvent was removed in vacuo and then purified by column chromatography (2.5% ether/97.5% pentane, anisaldehyde) to yield 11.5 g of product (34.2 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.74 (m, 4H), 7.55–7.38 (m, 6H), 6.33 (dd, J=15.0, 10.7, 1H), 6.23–6.06 (m, 1H), 5.83–5.66 (m, 2H), 4.32 (d, J=3.8, 2H), 1.83 (d, J=6.6, 3H), 1.16 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 133.9, 131.3, 130.4, 129.8, 129.6, 129.1, 127.8, 64.5, 27.0, 19.5, 18.3. IR (neat) 3023, 2932, 1959, 1824, 1472, 1427, 1380, 1112, 1050, 988, 823, 702, 606, 491 cm^{-1}. HRMS (EI$^+$) m/z 336.19001 [calculated mass for $C_{22}H_{28}OSi$ (M^+) 336.19095].

*2.1.10. Vinyl oxiranes **13** and **14**.* To a 500 mL flask equipped with a stir bar was added methylene chloride (320 mL), silyl ether **12** (12.2 g, 36.3 mmol), Na_2HPO_4 (9.81 g, equal mass with *m*-CPBA), and *m*-CPBA (70%, 9.81 g, 39.8 mmol, 1.1 equiv). After 1 h, the reaction was cooled to 0 °C and filtered through Celite washing with diethyl ether. It was then diluted with additional diethyl ether and washed with 1 M NaOH, a saturated $NaHCO_3$ solution, water, and dried over $MgSO_4$. The solvent was removed in vacuo to give a clear oil that was purified by column chromatography (2.5% ether/97.5% pentane, anisaldehyde). The regioisomeric vinyl oxirane products are readily separable and yielded 7.2 g of **13** and 5.5 g of **14** (1.3:1 ratio, 36.0 mmol, 99%). *Vinyl oxirane* **13**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 4H), 7.43–7.33 (m, 6H), 5.97 (ddd, J=15.5, 4.6, 4.1, 1H), 5.54 (ddt, J=15.4, 7.9, 1.9, 1H), 4.21 (dd, J=4.3, 1.8, 2H), 3.08 (dd, J=7.9, 2.1, 1H), 2.89 (qd, J=5.2, 2.2, 1H), 1.33 (d, J=5.2, 3H), 1.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 135.6, 134.1, 133.6, 133.5, 129.9, 127.9, 127.3, 63.7, 59.3, 56.6, 27.0, 19.4, 17.8. IR (neat) 2960, 2857, 1428, 1112, 963, 823, 703, 491 cm^{-1}. HRMS (EI$^+$) m/z 295.11565 [calculated mass for $C_{18}H_{19}O_2Si$ ($M-t$Bu$^+$) 295.11544]. *Vinyl oxirane* **14**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77–7.63 (m, 4H), 7.49–7.29 (m, 6H), 5.98–5.82 (m, 1H), 5.20 (ddq, J=15.3, 8.2, 1.6, 1H), 3.83 (dd, J=11.8, 3.5, 1H), 3.75 (dd, J=11.8, 4.5, 1H), 3.21 (dd, J=8.2, 2.1, 1H), 3.04 (ddd, J=4.5, 3.5, 2.2, 1H), 1.72 (dd, J=6.6, 1.6, 3H), 1.06 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8, 135.7, 133.4(4), 133.3(8), 132.0, 129.9, 128.3, 127.9(0), 127.8(9), 64.0, 60.1, 56.4, 26.9, 19.4, 18.1.

HRMS (EI^+) *m*/*z* 295.11522 [calculated mass for $C_{18}H_{19}O_2Si$ ($M-tBu^+$) 295.11544].

*2.1.11. 2,5-Dihydrofuran **15** from **13**.* To a flame dried 13×100 mm threaded culture tube was added vinyl oxirane **13** (25 mg, 0.071 mmol) in dry toluene (0.6 mL). The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150 °C. A syringe pump was used to add toluene over 10 h (0.1 mL, 0.01 mol %/hour), which contained $Cu(hfacac)_2$ (1.76 mg, 0.0035 mmol, 0.05 equiv). The solution was heated for a total of 12 h and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with ethyl acetate and then purified by flash chromatography on silica gel (2.5% ether/97.5% pentane, anisaldehyde) to yield of 2,5-dihydrofuran **15** (21 mg, 84%, 0.060 mmol), (Crude diastereomeric ratio >20:1, purified >20:1 *cis*/*trans*).

*2.1.12. 2,5-Dihydrofuran **15** from **14**.* To a flame dried 13×100 mm threaded culture tube was added vinyl oxirane **14** (25 mg, 0.071 mmol) in dry toluene (0.6 mL). The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150 °C. A syringe pump was used to add toluene over 10 h (0.1 mL, 0.01 mol %/hour), which contained $Cu(hfacac)_2$ (1.76 mg, 0.0035 mmol, 0.05 equiv). The solution was heated for a total of 12 h and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with ethyl acetate and then purified by flash chromatography on silica gel (2.5% ether/97.5% pentane, anisaldehyde) to yield 2,5-dihydrofuran **15** (20 mg, 80%, 0.057 mmol), (Crude diastereomeric ratio >20:1, purified >20:1 *cis*/*trans*). ^1H NMR (400 MHz, $CDCl_3$) δ 7.73–7.66 (m, 4H), 7.45–7.32 (m, 6H), 5.82 (s, 2H), 4.98–4.89 (m, 1H), 4.89–4.83 (m, 1H), 3.71 (dd, *J*=10.3, 4.9, 1H), 3.63 (dd, *J*=10.3, 5.4, 1H), 1.25 (d, *J*=6.4, 3H), 1.05 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9, 135.8, 133.9, 133.7, 132.7, 129.8(2), 129.7(8), 127.8, 127.5, 87.0, 82.5, 77.6, 77.2, 76.9, 67.7, 27.0, 23.0, 19.5. IR (neat) 2922, 2854, 1783, 1532, 1450, 1426, 1363, 1112, 1091, 912, 741, 701 cm^{-1}. HRMS (EI^+) *m*/*z* 295.11644 [calculated mass for $C_{18}H_{19}O_2Si$ ($M-tBu^+$) 295.11544].

*2.1.13. Diol **16**.* To a stirred flask containing acetone (4.5 mL), water (4.5 mL), dihydrofuran **15** (0.31 g, 0.88 mmol), and 4-methylmorpholine *N*-oxide (0.31 g, 2.64 mmol, 3 equiv) was added OsO_4 (2.5% in ^tBuOH, 1.0 mL, 0.1 equiv). After 12 h, the reaction was quenched with a solution of sodium bisulfite and diluted with ethyl acetate. The reaction was stirred vigorously for 16 h and then the layers were separated. The aqueous layer was extracted with ethyl acetate three additional times. The combined organic portions were dried over Na_2SO_4. The solvent was removed in vacuo and diol **15** was purified by chromatography (60% ether/40% pentane, anisaldehyde) to yield diol **16** (0.34 g 0.88 mmol, 99% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.77–7.60 (m, 4H), 7.53–7.30 (m, 6H), 4.20 (br s, 1H), 3.97–3.81 (m, 2H), 3.81–3.69 (m, 3H), 2.70 (bd, *J*=5.4, 1H), 2.63 (bd, *J*=3.1, 1H), 1.31 (d, *J*=6.2, 3H), 1.05 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8(4), 135.7(7), 133.4, 133.2, 130.0(2), 129.9(7), 127.9(7), 127.9(3), 84.2, 79.1, 76.9, 72.8, 64.5, 27.0, 19.4, 18.9. IR (neat) 3404, 2931, 2858, 1472, 1427, 1112, 1008, 938, 823, 702, 504 cm^{-1}. HRMS (ESI) *m*/*z* 409.1805 [calculated mass for $C_{22}H_{30}O_4NaSi$ ($M+Na^+$) 409.1811].

*2.1.14. Vinyl oxirane **19**.* To a 250 mL flask was added ethyl sorbate (1.0 g, 7.1 mmol, 1 equiv) and CH_2Cl_2 (50 mL). The solution was cooled to 0 °C and then (6.7 g, 71.1 mmol, 10 equiv) H_2O_2/Urea was added. Next, Na_2HPO_4 (9.1 g, 64 mmol, 9 equiv) was added followed by a slow addition of trifluoroacetic anhydride (2.5 mL, 3.75 g, 17.9 mmol, 2.5 equiv). The solution was vigorously stirred at 0 °C for 4 h. The reaction was decanted from the solid that aggregates during the course of the reaction. The solid was washed with CH_2Cl_2 and the organic washings are quenched with satd $NaHCO_3$. The organic layer was dried with Na_2SO_4 and the solvent removed in vacuo. The product was clean enough for further reaction but can be purified by silica gel chromatography (20% ether/80% pentane) to yield epoxide that was slightly volatile (0.88 g, 5.6 mmol, 80%). The product matched existing characterization data.[28]

*2.1.15. Vinyl oxiranes **20a** and **20b**.* To a tall threaded culture tube was added a stir bar, dry THF (1 mL), and LiHMDS (1.24 mL, 1.0 M in THF, 1.24 mmol, 1.02 equiv) The reaction was cooled to −78 °C and a solution of benzyl-2-bromoacetate (0.19 mL, 278 mg, 1.2 mmol, 1 equiv) in THF (0.5 mL) was added. The solution was stirred for 30 min at −78 °C and then crotonaldehyde (0.10 mL, 0.085 g, 1.2 mmol, 1 equiv) was added. The solution was stirred for 1 h at −78 °C and then the cooling bath was removed for 15 min before it was quenched with satd NH_4Cl. The reaction was extracted with CH_2Cl_2 and dried with Na_2SO_4. The product was purified by silica gel chromatography (10% ether/90% pentane, anisaldehyde) to yield of a 1.2:1 mixture of diasteriomers (**20b** *cis*/**20a** *trans*), (204 mg, 0.94 mmol, 77%). The products are separable by column chromatography to yield 60 mg of **20a** and 132 mg of **20b**. *Vinyl oxirane* **20a** ^1H NMR (400 MHz, $CDCl_3$) δ 7.40–7.31 (m, 5H), 6.03 (dq, *J*=15.4, 6.6, 1H), 5.34–5.08 (m, 3H), 3.56 (dd, *J*=8.2, 1.8, 1H), 3.40 (d, *J*=1.9, 1H), 1.75 (dd, *J*=6.6, 1.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8, 135.2, 134.5, 128.8, 128.7(4), 128.6(5), 126.3, 67.4, 58.4, 54.8, 18.1. IR (neat) 3032, 2962, 1748, 1763, 1454, 1424, 1278, 1186, 962, 763 cm^{-1}. HRMS (EI^+) *m*/*z* 218.09465 [calculated mass for $C_{13}H_{14}O_3$ (M^+) 218.09430]. *Vinyl oxirane* **20b** ^1H NMR (400 MHz, $CDCl_3$) δ 7.44–7.30 (m, 5H), 6.07 (dq, *J*=15.5, 6.6, 1H), 5.37 (ddq, *J*=15.5, 8.8, 1.7, 1H), 5.29 (d, *J*=12.1, 1H), 5.19 (d, *J*=12.2, 1H), 3.70 (d, *J*=4.5, 1H), 3.60 (dd, *J*=8.8, 4.5, 1H), 1.72 (dd, *J*=6.6, 1.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 136.1, 135.4, 128.8(4), 128.7(8), 128.7(5), 123.6, 67.36, 58.0, 54.5, 18.3. IR (neat) 3053, 2970, 1750, 1497, 1454, 1283, 1186, 967, 746, 698 cm^{-1}. HRMS (EI^+) *m*/*z* 218.09416 [calculated mass for $C_{13}H_{14}O_3$ (M^+) 218.09430].

*2.1.16. 2,5-Dihydrofuran **22** (trans).* To a flame dried 13×100 mm threaded culture tube was added vinyl oxiranes **20a** and **20b** (100 mg, 1:1.2, 0.45 mmol) in dry toluene (4.5 mL). Then, $Cu(hfacac)_2$ (23 mg, 0.046 mmol, 0.1 equiv) was added. The culture tube was fitted with a Teflon cap and submerged in an oil bath at 150 °C. After 2 h the reaction was concentrated and silica gel chromatography was performed (10% ether/90% pentane, anisaldehyde) to yield **22** (97 mg, 0.44 mmol, 97%, crude diastereomeric ratio 1:9, purified 1:9 *cis*/*trans*). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41–7.28 (m, 5H), 5.97–5.90 (m, 1H), 5.84 (dt, *J*=6.0, 2.1, 1H), 5.34 (dt, *J*=5.7, 2.1, 1H), 5.24–5.14 (m, 3H), 1.31 (d, *J*=6.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 135.7, 134.4, 128.7, 128.4, 128.3, 124.4, 84.1, 83.7, 66.8, 21.5. IR (neat) 2972, 2875, 1752, 1455, 1372, 1347, 1314, 1180, 1104, 1015, 745, 695 cm^{-1}. HRMS (EI^+) *m*/*z* 216.07782 [calculated mass for $C_{13}H_{12}O_3$ ($M-H_2^+$) 216.07865].

*2.1.17. Vinyl oxirane **24**.* To a 200 mL flame dried flask with magnetic stir bar was added methylene chloride (120 mL). To this solution was added (2*E*,4*E*,6*E*)-ethyl octa-2,4,6-trienoate[29] (2.00 g, 12.0 mmol, 1 equiv). Next, was added Na_2HPO_4 (2.7 g) followed by *m*-CPBA (2.7 g, 15.6 mmol, 1.3 equiv). The solution was stirred at room temperature until the starting material was consumed. The solution was cooled to 0 °C and then filtered through Celite. The organic filtrate was washed three times with satd $NaHCO_3$ and once with H_2O. The solution was dried with Na_2SO_4 and the solvent removed in vacuo. The product was purified by silica gel chromatography (15% ether/85% pentane) to yield vinyl oxirane **24** (1.73 g, 79%). ^1H NMR (500 MHz, C_6D_6) δ 7.36 (ddd, *J*=15.4, 11.2, 0.7, 1H),

6.07 (dd, J=15.3, 11.2, 1H), 5.87 (dd, J=15.4, 0.6, 1H), 5.34 (dd, J=15.3, 7.5, 1H), 4.05 (q, J=7.1, 2H), 2.62 (dd, J=7.5, 1.8, 1H), 2.42 (qd, J=5.1, 2.0, 1H), 0.99 (t, J=7.1, 3H), 0.94 (d, J=5.1, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 166.8, 143.5, 140.1, 131.1, 122.7, 60.6, 58.4, 57.1, 17.8, 14.7; IR (neat) 2984, 2932, 1713, 1644, 1619, 1305, 1231, 1145, 1000, 853 cm^{-1}; HRMS (EI$^+$) m/z 182.0941 [calculated mass for $C_{10}H_{14}O_3$ (M^+) 182.0943].

*2.1.18. 2,5-Dihydrofuran **25**.* To a flame dried 13×100 mm threaded culture tube was added vinyl oxirane **24** (25 mg, 0.14 mmol) in dry toluene (1 mL). The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150 °C. A syringe pump was used to add toluene over 17 h (0.5 mL, 0.12 mol %/hour), which contained Cu(hfacac)$_2$ (1.4 mg, 0.0027 mmol, 0.02 equiv). The solution was heated for a total of 24 h and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with ethyl acetate and then purified by flash chromatography on silica gel (20% ether/80% pentane, $KMnO_4$) to yield of 2,5-dihydrofuran **25** (21.0 mg, 84%, 0.12 mmol), (Crude diastereomeric ratio 8:1, purified >20:1 *cis*/*trans*). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.83 (dd, J=15.6, 5.3, 1H), 5.98 (d, J=15.5, 1H), 5.80–5.77 (m, 1H), 5.66 (d, J=6.0, 1H), 5.31–5.22 (m, 1H), 4.98–4.89 (m, 1H), 4.13 (q, J=7.2, 2H), 1.25 (d, J=6.4, 3H), 1.22 (t, J=7.2, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.7, 147.9, 132.6, 127.1, 120.7, 85.0, 83.1, 60.7, 22.9, 14.5; IR neat 2981, 2954, 2873, 1721, 1657, 1596, 1448, 1370, 1303, 1275, 1180, 1039, 981, 841 cm^{-1}; HRMS (EI$^+$) m/z 182.09420 [calculated mass for $C_{10}H_{14}O_3$ ($M+H^+$) 182.09430].

*2.1.19. Acetonide **26**.* To a stirred flask containing acetone (0.5 mL), water (0.5 mL), dihydrofuran **25** (0.014 g, 0.077 mmol), and 4-methylmorpholine *N*-oxide (9 mg, 0.077 mmol, 1 equiv) was added OsO_4 (2.5% in ^{t}BuOH, 0.01 mL, cat.). After 24 h, the reaction was quenched with a solution of sodium bisulfite and diluted with ethyl acetate. The reaction was stirred vigorously for several hours and then the layers were then separated. The aqueous layer was extracted with ethyl acetate three additional times. The combined organic portions were dried over Na_2SO_4. The solvent was removed in vacuo and the diol was purified by chromatography (70% ether/30% pentane, $KMnO_4$), (9.5 mg, 0.043 mmol, 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (dd, J=15.7, 4.8, 1H), 6.09 (dd, J=15.6, 1.7, 1H), 4.34–4.22 (m, 2H), 4.17 (q, J=7.1, 2H), 3.94–3.88 (m, 1H), 3.72 (at, J=5.2, 1H). 2.68 (bd, J=5.8, 1H), 2.47 (bd, J=5.5, 1H), 1.30 (d, J=6.3, 3H), 1.26 (t, J=7.1, 3H). The diol was prone to epimerization and retro aldol reactions and therefore it was protected immediately after purification. To a 4 mL reaction vial equipped with a stir bar was added the diol (34 mg, 0.16 mmol), methylene chloride (0.5 mL), pyridinium *p*-toluenesulfonate (0.01 g, 0.04 mmol, 0.25 equiv), and 2,2-dimethoxypropane (0.5 mL). The reaction was stirred for 12 h. It was diluted with methylene chloride and washed with $NaHCO_3$ and brine. The solution was dried over Na_2SO_4 and purified by chromatography (30% ether/70% pentane, $KMnO_4$) to give acetonide **26** (0.017 g, 0.066 mmol, 42% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (dd, J=15.7, 5.0, 1H), 6.11 (dd, J=15.7, 1.7, 1H), 4.49 (dd, J=6.8, 4.9, 1H), 4.44 (td, J=4.9, 1.7, 1H), 4.31 (dd, J=6.8, 4.4, 1H), 4.20 (q, J=6.5, 2H), 4.07 (qd, J=6.4, 4.5, 1H), 1.55 (s, 3H), 1.33 (s, 3H), 1.33 (d, J=6.5, 3H), 1.29 (t, J=7.1, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.3, 144.9, 122.2, 115.3, 86.3, 85.1, 83.2, 80.9, 60.7, 27.6, 25.7, 19.3, 14.4.

*2.1.20. Vinyl oxirane **30**.* To a 10 mL flask with a magnetic stir bar was added L-Proline (13 mg, 0.11 mmol, 0.2 equiv) followed by aldehyde **28** (0.1 g, 0.56 mmol, 1 equiv) in 1 mL of CH_2Cl_2. The solution was cooled to 0 °C and after 15 min *N*-chlorosuccinimide (0.097 g, 0.73 mmol, 1.3 equiv) was added. The solution was stirred for 2 h at 0 °C and then 1 h at room temperature, at which point it was quenched by the addition of pentane (5 mL) and filtered through a sintered glass funnel. The solvent was removed in vacuo and then resulting crude dissolved in pentane, filtered, and dried with Na_2SO_4. The solvent was removed once again to yield labile aldehyde **29**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (d, J=1.9, 1H), 7.40–7.28 (m, 5H), 4.50 (s, 2H), 4.45 (ddd, J=7.3, 5.3, 1.9, 1H), 3.75–3.58 (m, 2H), 2.37–2.28 (m, 1H), 2.13 (dddd, J=14.8, 7.5, 6.1, 4.3, 1H), 1.35–1.20 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.2, 138.0, 128.7, 128.0, 127.9, 73.4, 65.4, 61.7, 33.1. Aldehyde **29** was used without further purification. To another 10 mL round bottom flask was added THF (5 mL) and *E*-1-iodopropene (94 mg, 0.56 mmol, 1 equiv). The solution was cooled to −78 °C and then *n*-butyl-lithium (0.35 mL, 1.6 M in hexanes, 0.56 mmol, 1 equiv) was added dropwise. The solution was stirred for 10 min at −78 °C and then aldehyde **29** dissolved in THF (0.1 mL) was added. The solution was stirred for 15 min at −78 °C and then quenched with saturated NH_4Cl and diethyl ether. The solution was warmed to room temperature over 3 h. The solution was extracted with diethyl ether three times and then dried with Na_2SO_4. The solvent was removed to yield a mixture of epoxide and chloro-alcohol. This crude mixture was dissolved in absolute ethanol (5.6 mL). Then KOH (94 mg, 1.68 mmol, 3 equiv) was added and the solution was stirred for 30 min. The solution was quenched with brine and extracted with pentane. The organic layer was dried with Na_2SO_4 and the solvent removed. The epoxide was purified using silica gel chromatography (20% ether/80% pentane, anisaldehyde) to yield vinyl oxirane **30** (62 mg, 0.28 mmol, 51%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39–7.23 (m, 5H), 5.97–5.85 (m, 1H), 5.19 (ddd, J=15.4, 8.2, 1.7, 1H), 4.51 (s, 2H), 3.60 (dd, J=6.7, 5.8, 2H), 3.12 (dd, J=8.2, 2.2, 1H), 2.97 (ddd, J=6.8, 4.8, 2.2, 1H), 1.93 (dtd, J=11.7, 6.7, 4.8, 1H), 1.80 (ddd, J=11.9, 7.2, 4.0, 1H), 1.73 (dd, J=6.6, 1.7, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.4, 131.7, 128.8, 128.5, 127.7, 127.7, 73.2, 67.0, 58.8, 58.0, 32.7, 18.1. IR (neat) 2918, 2857, 1496, 1463, 1362, 1207, 1099, 963, 879, 734, 698 cm^{-1}. HRMS (EI$^+$) m/z 218.13117 [calculated mass for $C_{14}H_{18}O_2$ (M^+) 218.13068].

*2.1.21. 2,5-Dihydrofuran **31**.* To a flame dried 13×100 mm threaded culture tube was added vinyl oxirane **30** (10 mg, 0.046 mmol) in dry toluene (0.35 mL). The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150 °C. A syringe pump was used to add toluene over 10 h (0.1 mL, 0.1 mol %/hour), which contained Cu(hfacac)$_2$ (1.1 mg, 0.0022 mmol, 0.05 equiv). The solution was heated for a total of 13 h and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with ethyl acetate and then purified by flash chromatography on silica gel (10% ether/90% pentane, anisaldehyde) to yield 2,5-dihydrofuran **31** (7.0 mg, 70%, 0.032 mmol), (Crude diastereomeric ratio 10:1, purified >20:1 *cis*/*trans*). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.24 (m, 5H), 5.81–5.78 (m, 1H), 5.77–5.73 (m, 1H), 4.95–4.84 (m, 2H), 4.53 (d, J=11.8, 1H), 4.49 (d, J=11.8, 1H), 3.62 (dd, J=6.9, 6.0, 2H), 1.93 (dtd, J=12.0, 7.1, 4.9, 1H), 1.88–1.79 (m, 1H), 1.26 (d, J=6.3, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7, 131.6, 130.0, 128.6, 127.9, 127.7, 83.7, 81.9, 73.3, 67.4, 37.6, 23.2. HRMS (EI$^+$) m/z 218.13063 [calculated mass for $C_{14}H_{18}O_2$ (M^+) 218.13068].

*2.1.22. Diol **32**.* To a scintillation vial containing acetone (0.2 mL), water (0.2 mL), dihydrofuran **31** (0.005 g, 0.023 mmol), and 4-methylmorpholine *N*-oxide (8.1 mg, 0.069 mmol, 3 equiv) was added OsO_4 (2.5% in ^{t}BuOH, 0.1 mL, 0.3 equiv). After 12 h, the reaction was quenched with a solution of sodium bisulfite and diluted with ethyl acetate. The reaction was stirred vigorously for several hours and then the layers were separated. The aqueous layer was extracted with ethyl acetate three additional times. The combined organic portions were dried over Na_2SO_4. The solvent

was removed in vacuo and purified by chromatography (80% ether/20% pentane, anisaldehyde) to yield diol **32** (4.0 mg, 0.016 mmol, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.28 (m, 5H), 4.54 (d, J=1.1, 2H), 3.92–3.84 (m, 2H), 3.78–3.62 (m, 4H), 2.90 (bd, J=6.0, 1H), 2.76 (br s, 1H), 2.06–1.86 (m, 2H), 1.27 (d, J=6.5, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.4, 128.9, 128.3, 128.1, 82.1, 80.7, 76.7, 75.6, 73.8, 68.2, 34.1, 19.8. IR (neat) 3374, 2905, 2865, 1453, 1363, 1311, 1205, 1073, 1027, 882, 735, 697 cm^{-1}. HRMS (ESI) m/z 275.1251 [calculated mass for $C_{14}H_{20}O_4$ (M+Na$^+$) 275.1259].

*2.1.23. Primary alcohol **33**.* To a scintillation vial was added diol **32** (4 mg, 0.016 mmol, 1 equiv) and CH_2Cl_2 (0.3 mL). Then pyridinium *p*-toluenesulfonate (0.8 mg, 0.0032 mmol, 0.2 equiv) and 2,2-dimethoxypropane (16.5 mg, 0.158 mmol, 10 equiv) were added to the vial. The reaction was stirred for 12 h. It was diluted with methylene chloride and washed with $NaHCO_3$ and brine. The solution was dried over Na_2SO_4 and purified by chromatography (30% ether/70% pentane, anisaldehyde) to give the expected acetonide (2.0 mg, 0.0068 mmol, 43% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 4.56–4.47 (m, 2H), 4.43 (dd, J=7.0, 4.9, 1H), 4.23 (dd, J=7.0, 5.2, 1H), 3.96–3.86 (m, 2H), 3.67–3.56 (m, 2H), 1.94 (qd, J=13.8, 7.1, 2H), 1.53 (s, 3H), 1.33 (s, 3H), 1.29 (d, J=6.4, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7, 128.5, 127.8, 127.7, 115.0, 86.4, 85.6, 81.7, 80.2, 73.2, 67.2, 34.2, 27.6, 25.7, 19.2. HRMS (EI$^+$) m/z 292.16637 [calculated mass for $C_{17}H_{24}O_4$ (M$^+$) 292.16746]. To a small vial with a septum cap was added acetonide (0.8 mg, 0.0027 mmol). Then Pd/C (0.8 mg, 10%) was added along with methanol (0.5 mL). A balloon of hydrogen was attached to the vial and it was stirred at room temperature for 15 h. The solution was filtered through Celite and the solvent removed in vacuo to yield the primary alcohol **33** in quantitative yield (0.5 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44–4.37 (m, 1H), 4.28 (dd, J=7.1, 4.9, 1H), 3.99–3.90 (m, 2H), 3.84–3.78 (m, 2H), 2.33–2.27 (m, 1H), 1.99–1.90 (m, 1H), 1.90–1.79 (m, 1H), 1.54 (s, 3H), 1.34 (s, 3H), 1.32 (d, J=6.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 115.4, 86.2, 85.3, 84.0, 80.6, 61.2, 35.8, 27.6, 25.7, 19.3.

*2.1.24. Primary alcohol **34**.* To a 25 mL flask equipped with a stir bar was added methylene chloride (9 mL), diol **16** (0.340 g, 0.88 mmol), pyridinium *p*-toluenesulfonate (0.040 g, 0.16 mmol, 0.2 equiv), and dimethoxylcyclopentane (1.1 g, 8.5 mmol, 10 equiv). The reaction was stirred for 12 h at room temperature. It was diluted with methylene chloride and washed with $NaHCO_3$ and brine. The solution was dried over Na_2SO_4 and purified by chromatography (20% ether/80% pentane) to give cyclopenylacetal (0.297 g, 0.66 mmol, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.65 (m, 4H), 7.44–7.33 (m, 6H), 4.67 (dd, J=6.8, 3.7, 1H), 4.21 (dd, J=6.7, 5.1, 1H), 4.06–3.96 (m, 2H), 3.79 (d, J=3.9, 2H), 1.96 (t, J=7.6, 2H), 1.78–1.61 (m, 6H), 1.31 (d, J=6.3, 1H), 1.07 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.8(3), 135.7(6), 133.5, 133.3, 129.9, 129.8, 127.8(4), 127.7(9), 123.6, 86.1, 84.0, 82.4, 80.2, 64.4, 37.0, 36.9, 27.0, 23.7, 23.3, 19.4, 19.3. IR (neat) 2960, 2858, 1589, 1428, 1336, 1112, 979, 823, 702 cm^{-1}. To a 25 mL flask equipped with a stir bar was added cyclopentylacetal (0.297 g, 0.66 mmol) and tetrahydrofuran (6.5 mL). The solution was cooled to 0 °C and tetrabutylammonium fluoride (0.79 mL, 1 M in THF, 0.79 mmol, 1.2 equiv) was added dropwise. The reaction was stirred for 1 h at 0 °C and then 1 h at room temperature. The reaction was quenched with water and extracted with CH_2Cl_2. The solution was dried over Na_2SO_4 and purified by chromatography (50% ether/50% pentane) to give **34** (0.140 g, 0.65 mmol, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (dd, J=7.1, 4.5, 1H), 4.18 (dd, J=7.1, 5.2, 1H), 4.04–3.94 (m, 2H), 3.79 (dd, J=11.9, 3.4, 1H), 3.66 (dd, J=12.0, 4.7, 1H), 2.80 (br s, 1H), 1.96 (dd, J=11.1, 4.3, 2H), 1.76–1.62 (m, 6H), 1.31 (d, J=6.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 124.2, 86.0, 84.0, 81.6, 80.1, 62.7, 36.7(7), 36.7(5), 23.6, 23.2, 18.9. HRMS (EI$^+$) m/z 214.12064 [calculated mass for $C_{11}H_{18}O_4$ (M$^+$) 214.12051].

*2.1.25. Sulfone **35**.* To a 4 mL reaction vial containing dry methylene chloride (0.42 mL) and 1-phenyl-1*H*-tetrazole-5-thiol (0.045 g, 0.252 mmol) was added triphenylphosphine (0.066 g, 0.252 mmol) at 0 °C. Primary alcohol **34** (0.036 g, 0.168 mmol) was then dissolved in dry methylene chloride (0.23 mL) and added drop-wise to the above solution over 2 min. After complete addition, diisopropyl azodicarboxylate (DIAD) (0.05 mL, 0.252 mmol) was added slowly over 30 min by syringe and the reaction was allowed to stir an additional 90 min to consume all starting alcohol. The reaction was then concentrated to an oil and subsequently dissolved in ethanol (1.08 mL). To a 4 mL reaction vial containing ammonium molybdate (0.041 g, 0.033 mmol) was added 30% hydrogen peroxide solution (0.15 mL, 1.68 mmol) at 0 °C, which immediately turns yellow in color. The crude reaction mixture in ethanol was then added to the molybdate solution, the bath was removed and the reaction was allowed to stir 14 h at room temperature. The reaction was then quenched by adding saturated sodium sulfite solution (2 mL), extracted with dichloromethane and dried over anhydrous $NaSO_4$. The organics were concentrated and purified by flash chromatography (30% ethyl acetate/70% hexanes, anisaldehyde) to give sulfone **35** (0.055 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.55 (m, 5H), 4.47 (dd, J=6.8, 5.4, 1H), 4.27 (dd, J=12.3, 5.4, 1H), 4.19 (dd, J=6.8, 4.4, 1H), 3.94–3.88 (m, 3H), 1.95–1.87 (m, 2H), 1.73–1.60 (m, 6H), 1.13 (d, J=6.4, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.8, 133.0, 131.4, 129.5, 125.6, 125.0, 85.4, 83.6, 80.6, 77.5, 58.9, 36.6, 36.6, 23.5, 23.0, 18.7. IR (neat) 2973, 2941, 1498, 1353, 1154, 1106, 1054, 915, 764 cm^{-1}. HRMS (ESI) m/z 407.1389 [calculated mass for $C_{18}H_{23}N_4O_5S$ (M+H$^+$) 407.1389].

*2.1.26. Aldehyde **36**.* To a 50 mL flask was added the tribromide product derived from dimethyl anisole[30] (1.0 g, 2.68 mmol) and glacial acetic acid (16.0 mL) with a reflux condenser attached. To this was added sodium acetate (4.01 g, 29.49 mmol) and water (4.29 mL) and the reaction was refluxed at 110 °C for 7 h. After cooling to room temperature, the reaction was diluted with diethyl ether and washed with water, saturated bicarbonate, and sodium carbonate. The organics were dried over $NaSO_4$, concentrated, and purified using flash chromatography (30% ethyl acetate/70% hexanes, anisaldehyde) to give **36** (0.498 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.56–7.45 (m, 2H), 7.21–7.15 (m, 1H), 5.56 (s, 2H), 3.90 (s, 3H), 2.06 (s, 3H).^{13}C NMR (101 MHz, $CDCl_3$) δ 191.9, 170.9, 158.6, 136.1, 130.4, 125.1, 122.9, 116.4, 56.3, 56.0, 21.0. IR (neat) 2975, 2942, 2843, 1736, 1697, 1587, 1472, 1381, 1270, 1241, 1026. HRMS (EI$^+$) m/z 208.07384 [calculated mass for $C_{11}H_{12}O_4$ (M$^+$) 208.07356].

2.1.27. Protected varitriol. A fresh stock solution of potassium bis-(trimethylsilyl) amide (KHMDS) was prepared by mixing hexamethyldisilazane (0.051 mL, 0.24 mmol), dry tetrahydrofuran (5 mL), and 30% potassium hydride suspension (0.032 g, 0.24 mmol) at room temperature. To a 4 mL reaction vial was added sulfone **35** (0.020 g, 0.050 mmol) dissolved in a 4:1 mixture of dimethylformamide (DMF) and hexamethylphosphoramide (HMPA) (0.2 mL) at −78 °C. The freshly prepared KHMDS (1.0 mL, 0.048 mmol) was added and the reaction was allowed to stir 10 min. Aldehyde **36** (0.012 g, 0.055 mmol) was dissolved in the DMF/HMPA solvent mixture (0.2 mL) and subsequently added to the reaction. The reaction was allowed to slowly warm to room temperature and then stirred 12 h. The reaction was quenched by adding water (1 mL), extracted with diethyl ether, dried over $NaSO_4$, and purified by flash chromatography (30% ethyl acetate/70% hexanes, anisaldehyde) to give protected varitriol (0.018 g, 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J=8.0, 1H), 7.13 (d, J=8.0,

1H), 6.95 (d, J=15.7, 1H), 6.84 (d, J=8.0, 1H), 6.16 (dd, J=15.7, 6.4, 1H), 5.27 (s, 2H), 4.51–4.41 (m, 2H), 4.28 (dd, J=6.5, 4.6, 1H), 4.10–4.02 (m, 1H), 3.83 (s, 3H), 2.06 (s, 3H), 2.05–1.97 (m, 2H), 1.78–1.63 (m, 6H), 1.36 (d, J=6.4, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 158.6, 138.9, 131.0, 130.1, 129.6, 124.6, 121.5, 119.0, 110.3, 86.5, 85.8, 84.6, 80.2, 57.9, 56.1, 37.1, 37.0, 23.8, 23.4, 21.3, 19.4. IR (neat) 2970, 2943, 1735, 1580, 1473, 1379, 1242, 1102, 1054 cm^{-1}. HRMS (ESI) m/z 411.1770 [calculated mass for $C_{22}H_{28}O_6Na$ ($M+Na^+$) 411.1784].

2.1.28. Varitriol. To a 4 mL reaction vial was added protected varitriol (0.015 g, 0.039 mmol) and methanol (0.8 mL) at room temperature. To this was added solid sodium methoxide (0.010 g, 0.195 mmol) and the reaction was stirred for 1 h until starting material was consumed. At this time the reaction was filtered through a plug of silica gel with ethyl acetate to give crude primary alcohol. The crude primary alcohol was dissolved in methanol (0.6 mL) and Amberlyst **15** (5 mg) was added and the reaction was allowed to stir 1 h until starting material was consumed. The reaction was concentrated and filtered through a plug of silica gel with ethyl acetate to give varitriol (0.008 g, 74%), which matched all known spectral data in $(CD_3)_2CO$. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.20 (m, 1H), 7.14–7.02 (m, 2H), 6.83 (d, J=8.0, 1H), 6.13 (dd, J=15.7, 6.9, 1H), 4.87–4.72 (m, 2H), 4.34 (t, J=6.1, 1H), 3.99–3.89 (m, 2H), 3.87 (s, 3H), 3.83–3.75 (m, 1H), 2.58 (d, J=5.8, 1H), 2.43 (d, J=5.6, 1H), 2.21 (t, J=6.4, 1H), 1.37 (d, J=6.3, 3H).

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17. By using an acyl pyrrole variant of **17** instead of a t-butyl ester an asymmetric variant of **20** could be accessed following Shibasaki's impressive epoxidation protocol. (a) Kinoshita, T.; Okada, S.; Park, S.-R.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4680–4684; (b) Matsunaga, S.; Kinashita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559–7570.
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19. The fact that a mixture of *cis*- and *trans*-oxiranes **20** ring expanded to form *trans*-2,5-dihydrofuran **22** as the main product in excellent yield is noteworthy. We have recently demonstrated that *trans-E*- and *cis-E*- vinyl oxiranes can be stereoselectively ring expanded to *syn*- and *anti*-2,5-dihydrofurans, respectively. These studies did not uncover any epimerizations following ring expansion, but then again none of those substrates contained such an easily epimerizable group like the ester of vinyl oxirane **20**.[3]
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