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An olefination approach to the enantioselective syntheses of several styryllactones

Joel M. Harris and George A. O'Doherty*

Department of Chemistry, University of Minnesota, Minneapolis, MN 55455, USA

Dedicated to Professor Barry M. Trost on the occasion of his 60th birthday

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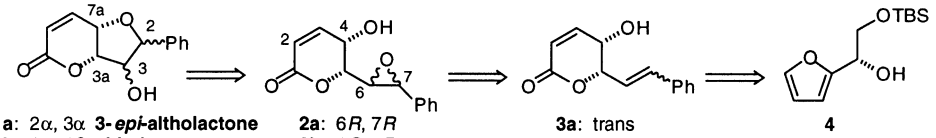
Abstract—A flexible enantioselective route to highly functionalized α,β-unsaturated δ-lactones, has allowed for the syntheses of the styryllactones: altholactone, isoaltholactone, 3-*epi*-altholactone, 2-*epi*-altholactone and 5-hydroxy goniothalamin in 2.5, 10, 5, 1 and 13% overall yields from furfural, respectively. This approach derives its asymmetry by applying the Sharpless catalytic asymmetric dihydroxylation to vinylfuran. The resulting diols are produced in high enantioexcess and can be stereoselectively transformed into α,β-unsaturated-δ-lactones via a short highly diastereoselective oxidation and reduction sequence. Wittig olefination or Julia olefination reactions were used to introduce the phenyl group side chain either *cis* or *trans* selectively and these intermediates were further elaborated into the altholactone isomers via selective epoxidation reactions.

Substituted α,β-unsaturated δ-lactones are an important class of natural products with a wide range of biological activity.[1] Many natural products from various plants and fungi share the common 5-oxygenated-5,6-dihydro-2*H*-pyran-2-one structural motif, such as goniodiol, acetylphomalactone, and altholactone.[1d] These natural products have biological activity including antitumor[1a] and antifungal properties,[1f] as well as antibiotic potential.[1f] Due to the wide distribution of 5,6-dihydro-2*H*-pyran-2-ones in plants and fungi, many synthetic methodologies have been employed to synthesize this core structure.[1,2]

As part of our synthetic efforts to enantioselectively synthesize biologically important *C*-arylglycoside natural products from achiral furans,[3] we chose to devise a route to the antitumor natural product altholactone **1b**. At the outset, we targeted a selective synthesis of the four possible C-2/C-3 diastereomers of altholactone **1a**–**d**. We opted for late installation of the arene ring, to allow for simple access to substituted arene analogs.

Altholactone, a furanopyrone member of the styryllactone family, was first isolated by Loder and Nearn[4] from the bark of an unnamed *Polyalthia* (Annonaceae) species, and has subsequently been isolated from various *Goniothalamus* species.[1a] Previous syntheses of altholactone have been accomplished by Gesson,[5] Shing,[6] Ogawa,[7] Kang,[8] Honda,[9] Somfai,[10] and Mukai[11] which range from 11 steps from D-gluconolactone[6] to 16 steps from D-glycerldehyde acetonide.[9] These syntheses derive their asymmetry from carbohydrate derivatives,[5–9] diethyl L-tartrate,[10] or a substituted benzaldehyde chromium (0) complex.[11]

Our approach to this class of natural products involves the synthesis of all four possible epoxide stereoisomers of epoxide **2**, which we envisioned would selectively cyclize to **1** upon acid treatment. We planned for a tunable and stereocontrolled epoxidation of both isomers of **3** to give all four possible isomers of **1**. Alternatively, a non-selective epoxidation of both double bond isomers of pyranone **3** could also provide all four stereoisomers of **2**. In turn, we



Scheme 1.

Keywords: Julia olefination; altholactone; Wittig olefination.

* Corresponding author. Tel.: +612-625-8862; fax: +612-626-7541; e-mail: odoherty@chem.umn.edu

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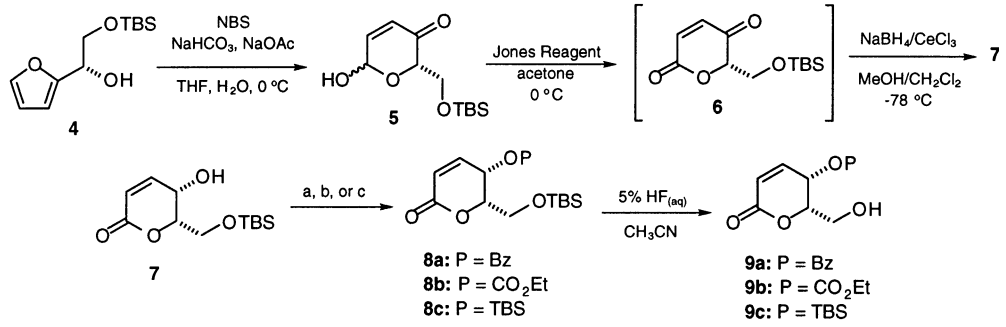
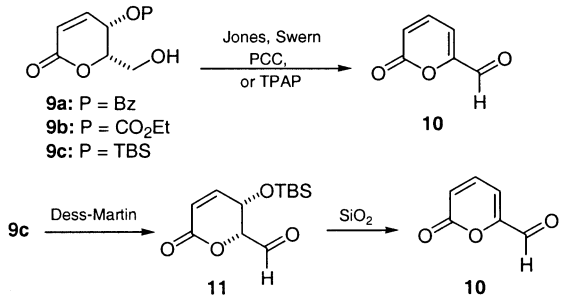


Scheme 2. (a) BzCl, pyr, CH_2Cl_2; (b) $ClCO_2Et$, pyr, CH_2Cl_2; (c) TBSOTf, 2,6-Lutidine, CH_2Cl_2.



Scheme 3.

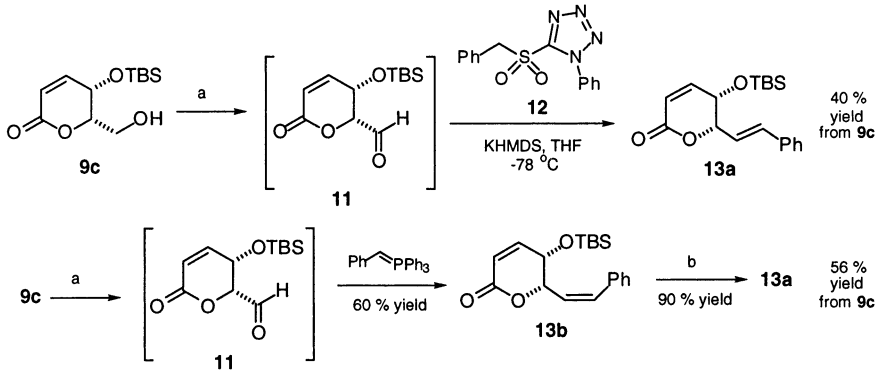
hoped to synthesize either double bond isomer of pyranone **3** via a selective Wittig or Julia olefination strategy (Scheme 1).

In our labs, we have developed a flexible route to various D- or L-sugars and sugar lactones from furan diols using Sharpless's dihydroxylation to establish the absolute stereochemistry.[12] Herein, we describe our continuing investigations[13] and results of this methodology applied to the syntheses of the altholactone diastereomers **1a–d** and 5-hydroxy goniothalamin **13a**.

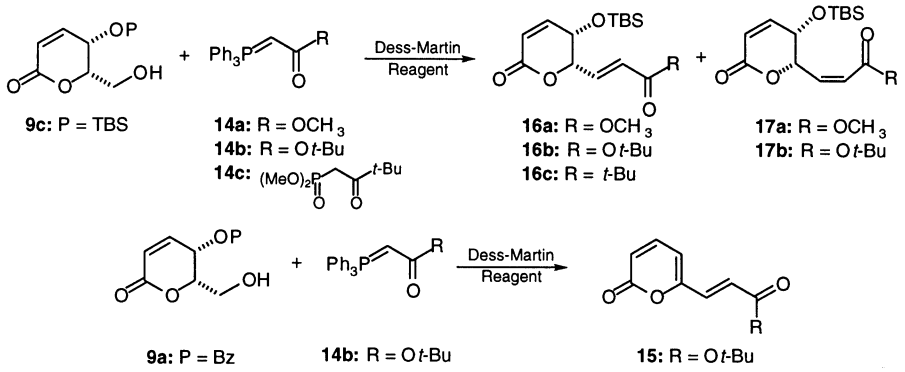
We envisioned synthesizing **3a** and **3b** from **4**, which we have previously prepared as either enantiomer from furfural in three steps and 75% overall yield.[13] Treatment of furyl alcohol **4** with NBS[14] in aqueous THF produces a hemiacetal pyranone **5** through an oxidative ring expansion (Achmatowicz reaction).[15] Treatment of the crude Achmatowicz product with excess Jones reagent gave ketolactone intermediate **6**, which was taken on without purification to a Luche reduction[16] with $NaBH_4$ and $CeCl_3$ in MeOH, to give δ-lactone **7**[17] in 70% yield from **5** and >92% ee.[18]

In order to gain access to a suitably protected aldehyde precursor necessary to install the olefin side chain, some protecting group manipulations were required (Scheme 2). Initial attempts included the use of a benzoyl or ethyl carbonate protecting group at C-4 (lactones **8a** and **8b**), however, C-4 carboxylate groups were incompatible with the ensuing oxidation step (**9** to **11**). The primary TBS group of **8a** and **8b** were cleanly deprotected with 5% HF in CH_3CN to give primary alcohols **9a** and **9b**. Unfortunately, oxidation of either alcohol **9a** or **9b** under various conditions (Jones, PCC, TPAP, and Dess–Martin) failed to give the desired aldehydes, only the elimination product **10** was formed (Scheme 3).

A practical solution was found by using a bis-TBS group protection strategy (Scheme 2). Protection of the free hydroxy group of lactone **7** was accomplished with TBSOTf forming **8c** in 90% yield. Selective deprotection of the primary TBS group of **8c** was accomplished with 5% HF in CH_3CN to exclusively give the free primary alcohol **9c** in 90% yield.[19] Dess–Martin oxidation of the primary alcohol gave the desired aldehyde **11** (Scheme 3), which was taken on without purification due to decomposition on silica gel. Although aldehyde **11** was unstable on silica gel, both Julia and Wittig olefination of crude **11** gave the desired δ-lactones **13a** and **13b** (Scheme 4). Treatment of aldehyde **11** generated from Dess–Martin oxidation of lactone **9c** with the anion of sulfone **12**[20] in THF at −78°C gave the



Scheme 4. (a) Dess–Martin periodinane, CH_2Cl_2, $NaHCO_3$, rt; (b) PhSH, 5% AIBN, PhH, reflux.

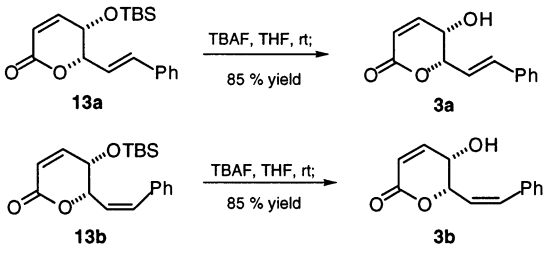


Scheme 5.

desired 1,2-*trans* alkene **13a** in 40% yield from **9c** and a diastereoselectivity of >13:1 in favor of the *trans* alkene. Under similar conditions the crude aldehyde **11** was converted into δ-lactone **13b** with the Wittig reagent (Ph_3P=CHPh) in a 60% yield and a diastereoselectivity of 7:1 in favor of the *cis* olefin at −78°C (Scheme 4).[21] δ-Lactone **13b** was isomerized to the *trans* isomer **13a** in a 90% yield using AIBN and PhSH in refluxing benzene.

A much simpler and higher yielding olefination procedure resulted from switching to the stabilized Wittig reagents **14a–c** (Scheme 5). Treating pyranone **9c** with 5 equiv. of **14a** in the presence of the Dess–Martin reagent (3 equiv.) yielded **16a** and **17a** as a 5:1 ratio and 88% yield.[22] Similarly, pyranone **9c** reacted with **14b** to give **16b** and **17b** in a 4:1 ratio and 65% yield. Reaction of aldehyde **11** with ketophosphonate **14c** and *t*-BuOK gave **16c** in 70% yield (>15:1 in favor of the *trans* isomer). Attempts to treat **9a** with **14b** in the presence of Dess–Martin reagent failed to give any of the desired product, instead only pyranone **15** in which the benzoyl group had eliminated was formed.

We next needed to find conditions to stereoselectivley epoxidize lactones **13a** and **13b** to obtain all four stereoisomers of **1a–d** in order to introduce the remaining oxygenation for the altholactone ring system. To achieve this selectively, we decided to investigate the epoxidation of both **3a** and **3b** as well as their TBS protected forms **13a** and **13b** (Scheme 6). Deprotection of both **13a** and **13b** proceeded smoothly upon the addition of TBAF (1 M in THF) to give styryllactones **3a** and **3b** in 85% yield. The deprotected product **3a** was identical in all regards to the styryl-pyranone natural product 5-hydroxy goniothalamin, which was formed in 10 steps from furfural and 13% overall yield.

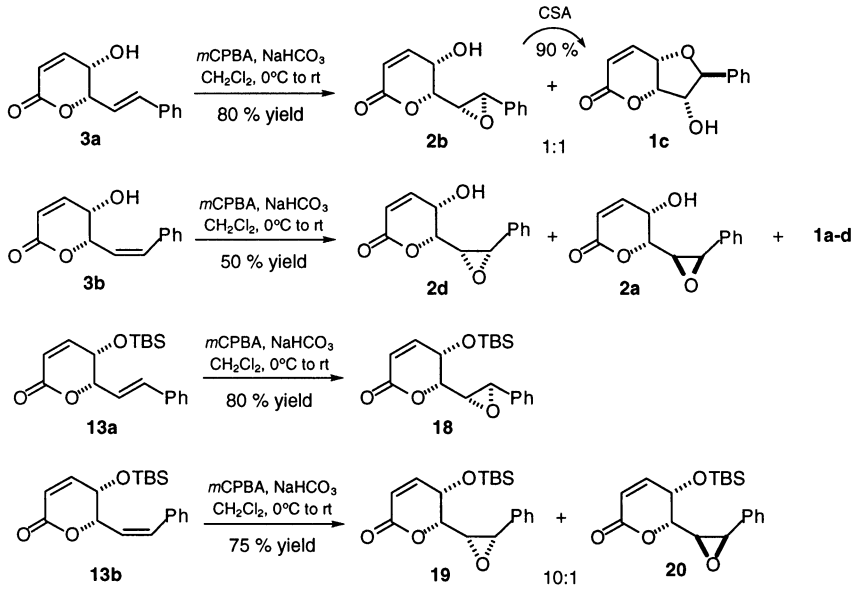


Scheme 6.

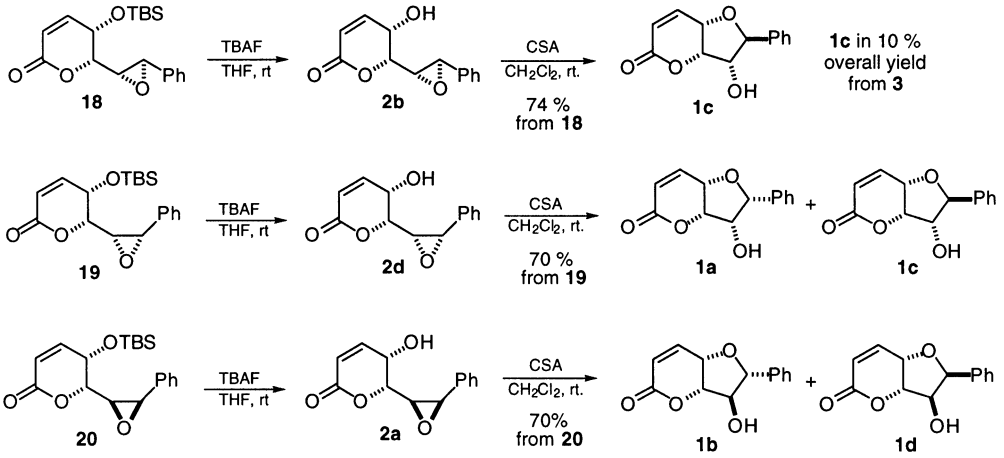
We first investigated the epoxidation of homoallylic alcohols **3a** and **3b** (Scheme 7). Treatment of the *trans* isomer **3a** with *m*-CPBA led to a good yield of a 1:1 mixture of epoxide **2b** (40%) and isoaltholactone **1c** (40%). The stereochemistry of **2b** was easily confirmed by acid catalyzed cyclization to **1c** in 90% yield using camphor sulfonic acid in methylene chloride. The stereochemistry of epoxide **2b** is consistent with a hydroxy directed epoxidation and formed as the single diastereomer shown (>15:1). The *cis* double bond, however, gave a complex mixture of epoxides **2d** and **2a** (approximately 4:1 ratio) and altholactones **1a–d** in 50% yield. The mixture was converted to all four altholactones **1a–d** using the previous acid catalyzed conditions, however, attempts to separate all four diastereomers by column chromatography failed to give diastereomerically pure samples.

In the hope of finding an increase in epoxidation selectivity, we investigated the epoxidation of the TBS-protected homoallylic alcohols **13a** and **13b** (Scheme 7). Treatment of **13a** with *m*-CPBA gave epoxide **18** as the major diastereomer (>15:1) in 85% yield. The stereochemistry of epoxidation was confirmed upon deprotection of the TBS group with TBAF (1 M in THF) providing **2b** in 85% yield (Scheme 8). As before, treating epoxide **2b** with CSA yielded isoaltholactone **1c** exclusively in 93% yield. The excellent stereoselectivity of this acid catalyzed epoxide opening of **2b** stands in contrast to the opening of **2d** which unfortunately gives a 1:1 mixture of altholactone diastereoisomers **1a** and **1c** in 90% yield. Isoaltholactone **1c** was synthesized in 10% overall yield and 12 steps from furfural with enantiomeric excess determined to be >91% ee by Mosher ester analysis.

Turning our attention to the *cis* isomer, **13b** was treated with *m*-CPBA yielding epoxides **19** and **20** in a ~10:1 ratio and 75% yield (Scheme 7). The stereochemistry of the epoxidation was assigned based on the stereochemistry of the final cyclized products. Deprotection of the TBS group in **19** was accomplished with TBAF, followed by acid promoted cyclization to give an inseparable 1:1 mixture of **1a** 3-*epi*-altholactone and **1c** isoaltholactone[23] in 70% yield over the last three steps which were inseparable by column chromatography. Conversion of **20** to altholactones **1b** and **1d** (1:1 ratio and 70% yield from **20**) was easily achieved using the previous conditions (TBAF followed by CSA) and were separable by column chromatography.

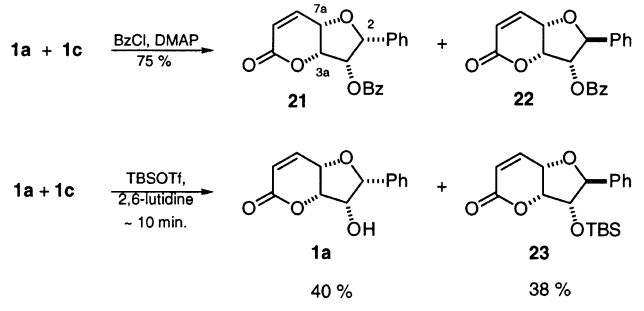


Scheme 7.



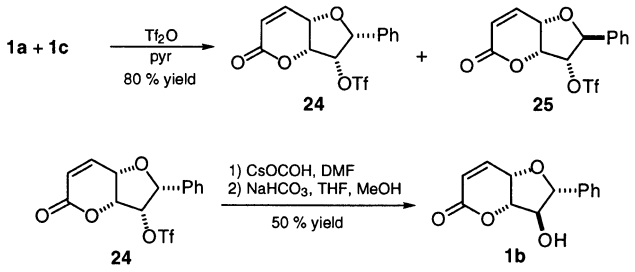
Scheme 8.

The inseparable mixture of **1a** 3-*epi*-altholactone and **1c** isoaltholactone were easily separated as benzoates **21** and **22**, which were prepared by treatment of a CH_2Cl_2 solution of **1a** and **1c** with BzCl and DMAP (Scheme 9). The relative stereochemistry of benzoates **21** and **22** were confirmed by a detailed nOe study. Particularly indicative for **21** were the enhancements between the hydrogen at C-2 to the bridgehead hydrogens at C-3a and C-7a, where as, for **22** no nOe enhancements were detected between the hydrogen at C-2 to the bridgehead hydrogens at C-3a and C-7a. A pure sample of **1a** was obtained upon treatment of the mixture of **1a** and **1c** with TBSOTf for 10 min to give a 40% yield of unprotected **1a** and a 38% yield of the TBS-protected isoaltholactone **23**.



Scheme 9.

The fact that benzoates **21** and **22** were easily separable, led us to explore the formation of triflates **24** and **25** (Scheme 10). Treatment of the mixture of **1a** and **1c** with Tf_2O and 2,6-lutidiene gave an 80% yield of triflates **24** and **25**. The triflates **24** and **25** were stable to and easily separated by silica gel chromatography. Displacement of the triflate group in **24** was facile using cesium formate[6b,24] in DMF giving the formate protected altholactone. Cleavage of the formate group was accomplished using saturated $NaHCO_3$ in THF and MeOH[25] to give **1b** in a 50% yield over the last two steps. Attempts to convert compound **25** to 3-*epi*-altholactone **1d** via displacement of the triflate with cesium formate have met with limited success, possibly due to steric hindrance of the phenyl substitution at C2.



Scheme 10.

In conclusion, this highly enantio- and diastereocontrolled route to α,β-unsaturated δ-lactones **3a** and **3b** allows access to a variety of styryllactone natural products including 5-hydroxy goniothalamin, altholactone, isoaltholactone, 2-*epi*-altholactone and 3-*epi*-altholactone in 13, 2.5, 10, 5 and 1% overall yields from furfural, respectively.[26] This methodology illustrates the utility of the enantioselective dihydroxylation reaction of vinylfuran, eliminating the need for kinetic resolution of 2-furylcarbinols. The route provides rapid and enantioselective access to α,β-unsaturated δ-lactones that are useful synthons for natural product synthesis from a commercially available, inexpensive starting material. Further studies on various epoxidation conditions and olefination reactions toward the synthesis of other natural products as well as biological evaluation of these diastereomers will be reported in due course.

1. Experimental

1.1. General methods

Unless otherwise stated, all reactions were carried out under an atmosphere of nitrogen using oven-dried glassware and standard syringe/septa techniques. Analytical TLC was performed using precoated glass-backed plates (Whatman K6F 60A, F_{254}) that were analyzed by fluorescence upon 254 nm irradiation or by staining with *p*-anisaldehyde, potassium permanganate, or phosphomolybdic acid stains. Liquid chromatography was performed using flash chromatography of the indicated solvent system on ICN reagent silica gel 60 (60–200 mesh). Ether and tetrahydrofuran were distilled from benzophenone and sodium metal. Dichloromethane and triethylamine were distilled from calcium hydride. Hexanes refers to the petroleum fraction bp 40–60°C. Commercial reagents were used without purification unless otherwise noted. ^{1}H and ^{13}C spectra were recorded on Varian 300 and 500 MHz spectrometers. Chemical shifts are reported relative to $CDCl_3$ (δ 7.26 ppm) or internal tetramethylsilane (δ 0.00 ppm) for ^{1}H and $CDCl_3$ (δ 77.0 ppm) for ^{13}C. Melting points are uncorrected. Optical rotations were measured with a Jasco DIP-370 digital polarimeter. Infrared (IR) spectra were obtained on a Prospect MIDAC FT-IR spectrometer. High resolution mass spectrometric data was performed by the University of Minnesota Mass Spectrometry Laboratory. Combustion analyses were performed by M-H-W Laboratories, Phoenix, AZ.

1.1.1. (6*S*)-6-*tert*-Butyldimethylsilanyloxymethylpyran-2,5-dione (6). Compound **5** (460 mg, 1.79 mmol) was dissolved in 15 mL of acetone and Jones reagent (2.5 M) was added at rt until a yellow color persisted. After 15 min the starting material was no longer visible by TLC and the solution was filtered through a pad of celite and washed with 100 mL of Et_2O. The Et_2O filtrate was washed with satd aq $NaHCO_3$ (50 mL) and the phases were separated. The organic layer was dried ($MgSO_4$) and concentrated to yield 367 mg (1.43 mmol, 80%) of pure dione **6**: R_f (20% EtOAc/hexanes)=0.40; $[\alpha]^{21}_D=-58.0$ (*c* 0.81, CH_2Cl_2); IR (thin film, cm^{-1}) 2949, 2928, 2892, 2857, 1721, 1697, 1461, 1360, 1306, 1261, 1128, 1111, 1083; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (d, *J*=10.0 Hz, 1H), 6.77 (d, *J*=10.0 Hz, 1H), 4.88 (dd, *J*=3.5, 3.5 Hz, 1H), 4.08 (dd, *J*=17.5, 3.5 Hz, 1H), 4.03 (dd, *J*=17.5, 4.5 Hz, 1H), 0.81 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.6, 160.5, 138.8, 136.2, 84.3, 65.2, 25.5, 18.0, −5.8, −5.9; CIHRMS Calcd for $[C_{12}H_{20}O_4Si+NH_4]^+$: 274.1475. Found: 274.1456; Anal. Calcd for C, 56.23; H, 7.87; Found C, 56.10; H, 7.68.

1.1.2. (6*S*)-6-*tert*-Butyldimethylsilanyloxymethyl-(5*S*)-5-hydroxy-5,6-dihydro-pyran-2-one (7). Compound **6** (870 mg, 3.39 mmol) was dissolved in 10 mL of CH_2Cl_2, cooled to −78°C with a dry ice/acetone bath, and 17 mL of a 0.4 M solution of $CeCl_3$ in MeOH was added to the solution. $NaBH_4$ (193 mg, 5.09 mmol) was added and the solution was stirred for 1.5 h. The solution was warmed to rt and 50 mL of Et_2O and 100 mL of H_2O were added. The phases were separated and the aq layer was extracted (5×50 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (20% EtOAc/hexanes) to give 840 mg (3.25 mmol, 96%) of compound **7**: R_f (20% EtOAc/hexanes)=0.28; $[\alpha]^{21}_D=+94.1$ (*c* 0.58, CH_2Cl_2); IR (thin film, cm^{-1}) 3416, 2930, 2857, 1713, 1631, 1472, 1383, 1258, 1138, 1098, 1059; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.00 (dd, *J*=9.5, 6.0 Hz, 1H), 6.12 (d, *J*=10.0 Hz, 1H), 4.41 (ddd, *J*=6.0, 6.0, 3.0 Hz, 1H), 4.37 (ddd, *J*=7.0, 4.5, 3.0 Hz, 1H), 4.09 (dd, *J*=10.5, 6.5 Hz, 1H), 4.03 (dd, *J*=11.0, 5.0 Hz, 1H), 3.10 (bs, 1H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 144.0, 123.0, 78.6, 62.1, 61.3, 25.7, 18.2, −5.5 (2C); CIHRMS Calcd for $[C_{12}H_{22}O_4Si+NH_4]^+$: 276.1631. Found: 276.1646; Anal. Calcd for C, 55.79; H, 8.59; Found C, 55.98; H, 8.39.

1.1.3. (6*S*)-6-*tert*-Butyldimethylsilanyloxymethyl-(5*S*)-5-benzoyl-5,6-dihydro-pyran-2-one (8a). Compound **7** (375 mg, 1.45 mmol) was dissolved in 5 mL of CH_2Cl_2 and (240 μL, 2.90 mmol) of pyridine was added to the solution. Benzoyl chloride (840 μL, 7.25 mmol) was added and the solution was stirred at rt for 3 h. The reaction was quenched with (10 mL) of satd aq $NaHCO_3$ and 10 mL of Et_2O. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (10% EtOAc/hexanes) to give 415 mg (1.14 mmol, 80%) of compound **8a**: R_f (10% EtOAc/hexanes)=0.3; $[\alpha]^{21}_D=+218.3$ (*c* 1.54, CH_2Cl_2); IR (thin film, cm^{-1}) 2955, 2929, 2884, 2856, 1724, 1452, 1266, 1136, 1095; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, *J*=8.0, 1.5 Hz, 2H), 7.59 (dt, *J*=8.5, 1.5, 1.5 Hz, 1H),

7.46 (dd, J=8.0, 1.5 Hz, 2H), 7.18 (dd, J=9.5, 6.0 Hz, 1H), 6.25 (d, J=10.0 Hz, 1H), 5.58 (dd, J=6.0, 2.5 Hz, 1H), 4.67 (ddd, J=8.5, 5.5, 2.5 Hz, 1H), 4.00 (dd, J=10.0, 8.5 Hz, 1H), 3.96 (dd, J=10.0, 5.5 Hz, 1H), 0.81 (s, 9H), 0.01 (s, 3H), −0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 162.2, 140.5, 133.6, 129.8, 128.6, 125.3, 78.4, 61.4, 60.2, 25.6, 18.0, −5.6, −5.8; FABHRMS Calcd for $[C_{19}H_{26}O_5Si+H]^+$: 363.1628. Found: 363.1624.

1.1.4. (6*S*)-6-*tert*-Butyldimethylsilanyloxymethyl-(5*S*)-5-ethoxycarbonyl-5,6-dihydro-pyran-2-one (8b). Compound **7** (32 mg, 0.12 mmol) was dissolved in 1.5 mL of CH_2Cl_2 and 100 μL of pyridine was added to the solution. Ethyl chloroformate (120 μL, 1.2 mmol) was added and the solution was stirred at rt for 8 h. The reaction was quenched with (10 mL) of satd aq $NaHCO_3$ and 10 mL of Et_2O. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (10% EtOAc/hexanes) to give 37 mg (0.11 mmol, 92%) of compound **8b**: R_f (10% EtOAc/hexanes)=0.28; $[\alpha]^{21}{}_D$=+189.9 (c 0.67, CH_2Cl_2); IR (thin film, cm^{-1}) 2958, 2931, 2886, 2857, 1747, 1472, 1372, 1341, 1256, 1136; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (dd, J=9.5, 6.0 Hz, 1H), 6.20 (d, J=9.5 Hz, 1H), 5.19 (dd, J=6.0, 3.0 Hz, 1H), 4.53 (ddd, J=8.5, 5.5, 2.5 Hz, 1H), 4.17 (dq, J=14.0, 7.0, 1.0 Hz, 2H), 3.91 (dd, J=10.0, 9.0 Hz, 1H), 3.86 (dd, J=10.0, 6.0 Hz, 1H), 1.28 (t, J=7.0 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.7, 154.1, 139.6, 125.6, 77.9, 64.6, 63.7, 59.8, 25.6, 18.0, 14.1, −5.7, −5.9; FABHRMS Calcd for $[C_{15}H_{26}O_6Si+H]^+$: 331.1577. Found: 331.1580; Anal. Calcd for C, 54.52; H, 7.94; Found C, 54.72; H, 8.04.

1.1.5. (6*S*)-6-*tert*-Butyldimethylsilanyloxymethyl-(5*S*)-5-*tert*-butyldimethylsilanyloxy-5,6-dihydro-pyran-2-one (8c). Compound **7** (70 mg, 0.27 mmol) was dissolved in 1.5 mL of CH_2Cl_2 and 125 μL (1.1 mmol) of 2,6-lutidine was added to the solution. TBSOTf (125 μL, 0.54 mmol) was added and the solution was stirred at 0°C for 0.5 h. The reaction was quenched with (10 mL) of satd aq $NaHCO_3$ and 10 mL of Et_2O. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (10% EtOAc/hexanes) to give 86 mg (0.23 mmol, 85%) of compound **8c**: R_f (10% EtOAc/hexanes)=0.25; $[\alpha]^{21}{}_D$=+124.0 (c 0.60, CH_2Cl_2); IR (thin film, cm^{-1}) 2954, 2929, 2886, 2857, 1715, 1472, 1383, 1253, 1115, 1069; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (dd, J=10.0, 5.5 Hz, 1H), 6.06 (d, J=9.5 Hz, 1H), 4.30 (dd, J=5.5, 2.5 Hz, 1H), 4.26 (ddd, J=8.0, 5.5, 3.0 Hz, 1H), 3.94 (dd, J=10.5, 8.0 Hz, 1H), 3.83 (dd, J=10.0, 5.0 Hz, 1H), 0.88 (s, 9H), 0.86 (s, 9H), 0.07 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 144.5, 122.6, 80.7, 60.4, 60.2, 25.8, 25.6, 18.2, 18.0, −4.2, −4.9, −5.43, −5.44; FABHRMS Calcd for $[C_{18}H_{36}O_4Si_2+Na]^+$: 395.2045. Found: 395.2045; Anal. Calcd for C, 58.03; H, 9.75; Found C, 57.99; H, 9.64.

1.1.6. (5*S*)-5-Benzoyl-(6*S*)-6-hydroxymethyl-5,6-dihydro-pyran-2-one (9a). Compound **8a** (29 mg, 0.080 mmol) was dissolved in 0.4 mL of CH_3CN and (270 μL, 0.23 mmol) of a 5% solution of aq HF (48%) in CH_3CN was added to the solution. The solution was stirred at rt for 4 h. The reaction was quenched with (10 mL) of satd aq $NaHCO_3$ and 10 mL of Et_2O. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (50% EtOAc/hexanes) to give 19 mg (0.077 mmol, 96%) of compound **9a**: mp=116–117°C; R_f (50% EtOAc/hexanes)=0.2; $[\alpha]^{21}{}_D$=+358.5 (c 0.40, CH_2Cl_2); IR (thin film, cm^{-1}) 3518, 3077, 2944, 2859, 1716, 1641, 1451, 1380, 1263, 1101, 1058; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (dd, J=8.0, 1.5 Hz, 2H), 7.62 (dt, J=9.0, 1.5, 1.5 Hz, 1H), 7.47 (dd, J=8.0, 1.5 Hz, 2H), 7.11 (dd, J=10.0, 6.0 Hz, 1H), 6.32 (d, J=10.0 Hz, 1H), 5.63 (dd, J=6.0, 3.0 Hz, 1H), 4.73 (ddd, J=9.0, 6.5, 2.5 Hz, 1H), 4.04 (ddd, J=12.5, 6.5, 6.0 Hz, 1H), 3.85 (ddd, J=12.0, 7.5, 6.5 Hz, 1H), 2.38 (dd, J=7.5, 6.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 162.1, 139.9, 134.0, 130.0, 128.7, 125.7, 79.1, 61.8, 60.6; FABHRMS Calcd for $[C_{13}H_{12}O_5+H]^+$: 249.0763. Found: 249.0774.

1.1.7. (5*S*)-5-*tert*-Butyldimethylsilanyloxy-(6*S*)-6-hydroxymethyl-5,6-dihydro-pyran-2-one (9c). Compound **8c** (140 mg, 0.376 mmol) was dissolved in 0.6 mL of CH_3CN and (0.6 mL, 0.56 mmol) of a 5% solution of aq HF (48%) in CH_3CN was added to the solution. The solution was stirred at rtfor 6 h. The reaction was quenched with (10 mL) of satd aq $NaHCO_3$ and 10 mL of Et_2O. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (50% EtOAc/hexanes) to give 88 mg (0.34 mmol, 91%) of compound **9c**: mp=93–95°C; R_f (50% EtOAc/hexanes)=0.3; $[\alpha]^{21}{}_D$=+149.4 (c 0.81, CH_2Cl_2); IR (thin film, cm^{-1}) 3367, 2957, 2928, 2856, 1710, 1462, 1385, 1257, 1117, 1070; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.83 (dd, J=10.0, 5.5 Hz, 1H), 6.11 (d, J=10.0 Hz, 1H), 4.44 (ddd, J=8.0, 5.0, 3.0 Hz, 1H), 4.33 (dd, J=5.5, 3.0 Hz, 1H), 4.02 (ddd, J=12.0, 7.0 Hz, 1H), 3.85 (dd, J=12.0, 6.0 Hz, 1H), 2.14 (bs, 1H), 0.87 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 144.0, 122.6, 80.9, 61.6, 61.5, 25.5, 18.0, −4.2, −5.0; FABHRMS Calcd for $[C_{12}H_{22}O_4Si+H]^+$: 259.1366. Found: 259.1380; Anal. Calcd for C, 55.79; H, 8.42; Found C, 55.83; H, 8.42.

1.1.8. 6-oxo-6*H*-Pyran-2-carbaldehyde (10). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.55 (s, 1H), 7.47 (dd, J=15.5, 10.5 Hz, 1H), 6.91 (dd, J=10.5, 2.0 Hz, 1H), 6.61 (dd, J=16.0, 2.0 Hz, 1H).

1.1.9. (3*S*)-3-*tert*-Butyldimethylsilanyloxy-6-oxo-3,6-dihydro-2*H*-pyran-(2*S*)-2-carbaldehyde (11). Compound **9c** (172 mg, 0.665 mmol) was dissolved in 3.0 mL of CH_2Cl_2 and (850 mg, 10.1 mmol) of $NaHCO_3$ and (850 mg, 2.00 mmol) of Dess–Martin reagent were added to the solution. The solution was stirred at rt for one hour. The reaction was quenched with 20 mL of Et_2O. The solution was filtered through florisil and subsequent washing of the florisil with 100 mL of Et_2O. The organic fraction was

concentrated to give crude **11**, 140 mg (0.527 mmol, 80%): R_f (100% Et_2O)=0.3; IR (thin film, cm^{-1}) 2957, 2929, 2896, 2858, 1724, 1472, 1463, 1380, 1255, 1123, 1084; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (s, 1H), 6.80 (dd, J=9.9, 4.5 Hz, 1H), 6.12 (d, J=9.6 Hz, 1H), 4.71 (m, 2H), 0.84 (s, 9H), 0.09 (s, 3H), 0.086 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 161.3, 143.3, 122.5, 83.2, 62.8, 25.4, 17.9, −4.4, −5.1; CIHRMS Calcd for $[C_{12}H_{20}O_4Si+H]^+$: 257.1209. Found: 257.1218.

1.1.10. (5*S*)-5-*tert*-Butyldimethylsilanyloxy-(6*S*)-6-*trans*-styryl-5,6-dihydro-pyran-2-one (13a). Sulfone tetrazole **12** (342 mg, 1.14 mmol) was dissolved in 1.0 mL of THF and (0.76 mL, 0.57 mmol) of 0.75 M KHMDS was added to the solution at 0°C. The solution was stirred at rt for 20 min. The solution was cooled to −78°C and compound **11** (146 mg, 0.57 mmol) in 2.5 mL of THF was syringed into the solution. The solution was stirred at −78°C for 3 h and another 8 h at rt. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (20% EtOAc/hexanes) to give **13a**, 75 mg (0.228 mmol, 40% over two steps): R_f (20% EtOAc/hexanes)=0.18; $[\alpha]^{21}_D$=+95.0 (*c* 1.85, CH_2Cl_2); IR (thin film, cm^{-1}) 3057, 2954, 2929, 2857, 1724, 1496, 1472, 1381, 1252, 1155, 1101, 1047; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.30 (m, 5H), 6.83 (dd, J=10.0, 5.0 Hz, 1H), 6.74 (d, J=16.0 Hz, 1H), 6.37 (dd, J=16.0, 7.0 Hz, 1H), 6.09 (d, J=10.0, 9.5 Hz, 1H), 4.98 (ddd, J=7.0, 4.5, 1.0 Hz, 1H), 4.37 (dd, J=4.5 Hz, 1H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1, 145.3, 135.9, 134.4, 128.7, 128.2, 126.7, 122.9, 121.9, 81.4, 64.3, 25.6, 18.0, −4.5, −4.8; FABHRMS Calcd for $[C_{12}H_{20}O_3Si+H]^+$: 331.1729. Found: 331.1758; Anal. Calcd for C, 69.06; H, 7.94; Found C, 69.25; H, 7.54.

1.1.11. (5*S*)-5-*tert*-Butyldimethylsilanyloxy-(6*S*)-6-*cis*-styryl-5,6-dihydro-pyran-2-one (13b). Benzyl triphenylphosphonium bromide (100 mg, 0.228 mmol) was dissolved in 0.5 mL of THF and (115 μL, 0.182 mmol) of *n*-BuLi was added to the solution at 0°C. The solution was stirred at rt for 20 min. The solution was cooled to −78°C and compound **11** (39 mg, 0.152 mmol) in 0.5 mL of THF was syringed into the benzylidene triphenyl phosphorane solution. The solution was stirred at −78°C for 30 min. The reaction was warmed to rt, quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (20% EtOAc/hexanes) to give **13b**, 21 mg (0.064 mmol, 60% over two steps): mp=144–147°C; R_f (20% EtOAc/hexanes)=0.25; $[\alpha]^{21}_D$=−16.4 (*c* 0.97, CH_2Cl_2); IR (thin film, cm^{-1}) 2928, 2855, 1715, 1463, 1443, 1384, 1360, 1277, 1256, 1101, 1080; ^1H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 2H), 7.29 (m, 3H), 6.88 (d, J=11.5 Hz, 1H), 6.81 (dd, J=9.5, 5.0 Hz, 1H), 6.07 (d, J=9.5 Hz, 1H), 6.04 (dd, J=11.5, 9.5 Hz, 1H), 5.15 (dd, J=9.5, 3.0 Hz, 1H), 4.25 (dd, J=4.5, 3.0 Hz, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.2, 145.1, 135.9, 135.6, 128.53, 128.50, 127.8, 124.9, 122.1, 76.8, 63.7, 25.6, 18.1, −4.4, −4.8; FABHRMS Calcd for $[C_{12}H_{20}O_3Si+H]^+$: 331.1729. Found: 331.1725; Anal. Calcd for C, 69.06; H, 7.94; Found C, 68.85; H, 7.76.

1.1.12. (3*S*)-[3-*tert*-Butyldimethylsilanyloxy-6-oxo-3,6-dihydro-2*H*-pyran-2*S*-yl]-*trans*-acrylic acid methyl ester (16a). Compound **9c** (100 mg, 0.39 mmol) was dissolved in 4 mL of CH_2Cl_2 and Dess–Martin periodinane (492 mg, 1.16 mmol) and compound **14a** (648 mg, 1.94 mmol) were added to the solution. The reaction was stirred for 12 h at rt. The reaction was quenched with 50 mL of Et_2O, filtered through a pad of celite and an extra 100 mL of Et_2O to wash the pad of celite. The crude product was purified silica gel chromatography eluting with (30% EtOAc/hexanes) to give a 5:1 ratio of compounds **16a** (90 mg, 0.29 mmol) and **17a** (17 mg, 0.054 mmol) in an 88% overall yield: R_f (30% EtOAc/hexanes)=0.24; $[\alpha]^{21}_D$=+139.3 (*c* 0.95, CH_2Cl_2); IR (thin film, cm^{-1}) 2953, 2931, 2887, 1734, 1669, 1436, 1380, 1310, 1249, 1177, 1108, 1049; ^1H NMR (500 MHz, $CDCl_3$) δ 6.93 (dd, J=16.0, 5.0 Hz, 1H), 6.78 (dd, J=10.0, 5.0 Hz, 1H), 6.20 (dd, J=16.0, 2.0 Hz, 1H), 6.03 (d, J=10.0 Hz, 1H), 4.99 (ddd, J=4.5, 4.0, 2.0 Hz, 1H), 4.42 (dd, J=4.0, 4.0 Hz, 1H), 3.73 (s, 3H), 0.83 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 162.0, 145.1, 140.7, 123.7, 121.7, 79.0, 63.3, 51.7, 25.4, 17.9, −4.6, −5.0; FABHRMS Calcd for $[C_{15}H_{24}O_5Si+H]^+$: 313.1471. Found: 313.1465.

1.1.13. (3*S*)-[3-*tert*-Butyldimethylsilanyloxy-6-oxo-3,6-dihydro-2*H*-pyran-2*S*-yl]-*cis*-acrylic acid methyl ester (17a). R_f (30% EtOAc/hexanes)=0.51; $[\alpha]^{21}_D$=+17.9 (*c* 0.90, CH_2Cl_2); IR (thin film, cm^{-1}) 2955, 2930, 2857, 1740, 1720, 1472, 1438, 1250, 1107, 1059; ^1H NMR (500 MHz, $CDCl_3$) δ 6.86 (dd, J=9.5, 5.5 Hz, 1H), 6.42 (dd, J=12.0, 7.5 Hz, 1H), 6.11 (d, J=10.0 Hz, 1H), 6.01 (dd, J=11.5, 1.5 Hz, 1H), 5.91 (ddd, J=7.5, 3.0, 1.5 Hz, 1H), 4.52 (dd, J=5.5, 2.5 Hz, 1H), 3.74 (s, 3H), 0.84 (s, 9H), 0.03 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.0, 162.8, 144.7, 144.3, 122.2, 121.1, 78.1, 62.6, 51.7, 25.5, 17.9, −4.3, −5.0; FABHRMS Calcd for $[C_{15}H_{24}O_5Si+H]^+$: 313.1471. Found: 313.1486.

1.1.14. (3*S*)-[3-*tert*-Butyldimethylsilanyloxy-6-oxo-3,6-dihydro-2*H*-pyran-2*S*-yl]-*trans*-acrylic acid *tert*-butyl ester (16b). Compound **9c** (137 mg, 0.53 mmol) was dissolved in 4 mL of CH_2Cl_2 and Dess–Martin periodinane (680 mg, 1.60 mmol) and compound **14b** (670 mg, 1.70 mmol) were added to the solution. The reaction was stirred for 12 h at rt. The reaction was quenched with 50 mL of Et_2O, filtered through a pad of celite and an extra 100 mL of Et_2O to wash the pad of celite. The crude product was purified silica gel chromatography eluting with (20% EtOAc/hexanes) to give a 4:1 ratio of compounds **16b** (98 mg, 0.28 mmol) and **17b** (24 mg, 0.068 mmol) in a 65% overall yield: R_f (20% EtOAc/hexanes)=0.30; $[\alpha]^{21}_D$=+10.8 (*c* 2.70, CH_2Cl_2); IR (thin film, cm^{-1}) 2931, 2858, 1731, 1472, 1368, 1299, 1251, 1155, 1097, 1056; ^1H NMR (500 MHz, $CDCl_3$) δ 6.85 (dd, J=16.0, 5.0 Hz, 1H), 6.79 (dd, J=10.0, 4.5 Hz, 1H), 6.12 (dd, J=15.5, 1.5 Hz, 1H), 6.07 (d, J=9.5 Hz, 1H), 4.98 (ddd, J=4.5, 4.0, 2.0 Hz, 1H), 4.39 (dd, J=4.0, 4.0 Hz, 1H), 1.48 (s, 9H), 0.87 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 164.7, 162.2, 144.9, 139.2, 126.1, 121.2, 80.8, 79.20, 79.16, 28.0, 25.5, 17.9, −4.5, −5.0; FABHRMS Calcd for $[C_{18}H_{30}O_5Si+H]^+$: 355.1941. Found: 355.1926.

1.1.15. (5*S*)-5-(*tert*-Butyldimethylsilanyloxy)-(6*S*)-6-(4,4-dimethyl-3-oxo-pent-(1*E*)-1-enyl)-5,6-dihydro-pyran-2-one (16c). Compound **14c** (51 mg, 0.235 mmol) was dissolved in 0.5 mL of THF and *t*-BuOK (26 mg, 0.235 mmol) was added to the solution at −78°C. The solution was stirred for 20 min. Compound **11** (55 mg, 0.21 mmol) in 0.5 mL of THF was syringed into the solution and an extra 1 mL of THF was used to transfer compound **11**. The solution was stirred at −78°C for 3 h. The reaction was warmed to rt, quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (20% EtOAc/hexanes) to give **16c**: R_f (30% EtOAc/hexanes)=0.31; $[\alpha]^{21}_D$=+156.2 (*c* 2.50, CH_2Cl_2); IR (thin film, cm^{-1}) 2955, 2929, 2858, 1714, 1688, 1634, 1475, 1463, 1365, 1302, 1259, 1097, 1073; ^1H NMR (500 MHz, C_6D_6) δ 7.02 (dd, *J*=15.0, 2.0 Hz, 1H), 6.84 (dd, *J*=15.5, 3.5 Hz, 1H), 5.94 (dd, *J*=9.5, 4.5 Hz, 1H), 5.55 (d, *J*=10.0 Hz, 1H), 4.32 (ddd, *J*=3.5, 3.0, 2.0 Hz, 1H), 3.43 (dd, *J*=4.5, 3.0 Hz, 1H), 1.00 (s, 9H), 0.79 (s, 9H), −0.12 (s, 3H), −0.17 (s, 3H); ^{13}C NMR (75 Hz, $CDCl_3$) δ 203.4, 162.6, 145.2, 138.6, 125.8, 122.0, 79.6, 63.2, 43.3, 26.0, 25.6, 18.0, −4.4, −4.8; FABHRMS Calcd for $[C_{18}H_{30}O_4Si+Na]^+$: 361.1811. Found: 361.1811.

1.1.16. 5-Hydroxy-goniothalamin (3a). Compound **13a** (5.5 mg, 0.017 mmol) was dissolved in 0.2 mL of THF and 30 μL (0.030 mmol) of a 1.0 M solution of TBAF was added to the solution at rt. The reaction was stirred for 0.5 h at rt. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (100% Et_2O) to give **14**, 3.1 mg (0.014 mmol, 85%): R_f (100% Et_2O)=0.25; $[\alpha]^{21}_D$=+62.4 (*c* 0.12, CH_2Cl_2); IR (thin film, cm^{-1}) 3386, 2924, 2854, 1712, 1450, 1377, 1253, 1085, 1037; ^1H NMR (500 MHz, $CDCl_3$) δ 7.46–7.32 (m, 5H), 7.04 (dd, *J*=9.6, 5.4 Hz, 1H), 6.88 (dd, *J*=15.3, 1.0 Hz, 1H), 6.37 (dd, *J*=15.9, 6.3 Hz, 1H), 6.19 (d, *J*=9.9 Hz, 1H), 5.08 (ddd, *J*=6.6, 3.0, 1.5 Hz, 1H), 4.33 (dd, *J*=5.7, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9, 144.3, 135.3, 128.7, 128.6, 126.8, 125.5, 123.1, 121.4, 80.9, 63.1; FABHRMS Calcd for $[C_{13}H_{12}O_3+H]^+$: 217.0865. Found: 217.0880.

1.1.17. (5*S*)-5-Hydroxy-(6*S*)-6-*cis*-styryl-5,6-dihydro-pyran-2-one (3b). Compound **13b** (90 mg, 0.272 mmol) was dissolved in 1.5 mL of THF and 0.275 mL (0.275 mmol) of a 1.0 M solution of TBAF was added to the solution at rt. The reaction was stirred for 0.5 h at rt. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (100% Et_2O) to give **3b**, 50 mg (0.23 mmol, 85%): R_f (100% Et_2O)=0.3; $[\alpha]^{21}_D$=−145.9 (*c* 0.26, CH_2Cl_2); IR (thin film, cm^{-1}) 3386, 2925, 2854, 1712, 1494, 1378, 1254, 1152, 1073, 1036; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40–7.27 (m, 5H), 6.98 (dd, *J*=9.6, 5.4 Hz, 1H), 6.96 (d, *J*=11.4 Hz, 1H), 6.15 (d, *J*=9.6 Hz, 1H), 6.09 (d, *J*=11.7, 9.6 Hz, 1H), 5.25 (ddd, *J*=9.6, 3.0, 0.9 Hz, 1H), 4.25 (ddd, *J*=8.7, 5.7, 3.3 Hz, 1H), 1.87 (d, *J*=8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.6, 144.4, 136.8, 135.6, 128.6, 128.5, 128.0, 123.6, 122.9, 77.2, 63.1; CIHRMS Calcd for $[C_{13}H_{12}O_3+NH_4]^+$: 234.1130. Found: 234.1135.

1.1.18. (5*S*)-5-*tert*-Butyldimethylsilanyloxy-(6*S*)-6-((2*S*,3*R*)-3-phenyloxiranyl)-5,6-dihydro-pyran-2-one (18). Compound **13a** (37 mg, 0.112 mmol) was dissolved in 1.1 mL of CH_2Cl_2, $NaHCO_3$ (60 mg, 0.67 mmol) and *m*-CPBA (39 mg, 0.22 mmol) were added to the solution. The reaction was stirred for 8 h at rt. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (20% EtOAc/hexanes) to give **18**, 30 mg (0.087 mmol, 78%): R_f (20% EtOAc/hexanes)=0.15; $[\alpha]^{21}_D$=+74.3 (*c* 0.70, CH_2Cl_2); IR (thin film, cm^{-1}) 2929, 2857, 1736, 1478, 1380, 1252, 1113, 1063; ^1H NMR (500 MHz, $CDCl_3$) δ 7.44–7.26 (m, 5H), 6.91 (dd, *J*=10.0, 5.5 Hz, 1H), 6.13 (d, *J*=9.5 Hz, 1H), 4.42 (dd, *J*=6.0, 3.0 Hz, 1H), 4.10 (dd, *J*=7.0, 3.0 Hz, 1H), 3.96 (d, *J*=2.0 Hz, 1H), 3.44 (dd, *J*=6.5, 1.5 Hz, 1H), 0.89 (s, 9H), 0.17 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 144.0, 129.8, 128.6, 128.5, 125.7, 122.6, 80.9, 61.2, 58.8, 58.3, 25.6, 18.0, −4.4, −4.9; FABHRMS Calcd for $[C_{19}H_{26}O_4Si+H]^+$: 347.1679. Found: 347.1686.

1.1.19. (5*S*)-5-*tert*-Butyldimethylsilanyloxy-(6*S*)-6-((2*S*,3*S*)-3-phenyloxiranyl)-5,6-dihydro-pyran-2-one (19). Compound **13b** (119 mg, 0.360 mmol) was dissolved in 3.5 mL of CH_2Cl_2, $NaHCO_3$ (311 mg, 3.7 mmol) and *m*-CPBA (311 mg, 1.8 mmol) were added to the solution. The reaction was stirred for 8 h at rt. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (20% EtOAc/hexanes) to give **19** (90 mg, 0.26 mmol) and **20** (9 mg, 0.026 mmol) in a 75% overall yield. Compound **19**: mp=110–112°C; R_f (20% EtOAc/hexanes)=0.25; $[\alpha]^{21}_D$=+98.6 (*c* 0.59, CH_2Cl_2); IR (thin film, cm^{-1}) 2952, 2927, 2855, 1722, 1462, 1379, 1254, 1158, 1104, 1061; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37–7.31 (m, 5H), 6.83 (dd, *J*=9.5, 6.0 Hz, 1H), 5.99 (d, *J*=10.0 Hz, 1H), 4.32 (d, *J*=4.0 Hz, 1H), 4.26 (dd, *J*=5.5, 2.5 Hz, 1H), 3.65 (dd, *J*=9.0, 3.5 Hz, 1H), 3.62 (dd, *J*=9.0, 2.5 Hz, 1H), 0.92 (s, 9H), 0.21 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 143.7, 133.9, 128.4, 128.2, 126.4, 122.7, 76.6, 61.5, 57.4, 55.0, 25.6, 18.1, −4.3, −5.0; FABHRMS Calcd for $[C_{19}H_{26}O_4Si+H]^+$: 347.1679. Found: 347.1686.

1.1.20. (5*S*)-5-*tert*-Butyldimethylsilanyloxy-(6*S*)-6-((2*R*,3*R*)-3-phenyloxiranyl)-5,6-dihydro-pyran-2-one (20). Compound **20**: mp=112–115°C; R_f (20% EtOAc/hexanes)=0.15;

$[\alpha]^{21}_D$=+61.6 (*c* 0.45, CH_2Cl_2); IR (thin film, cm^{-1}) 2940, 2872, 1727, 1453, 1372, 1254, 1076; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.33 (m, 5H), 6.60 (dd, *J*=9.5, 5.0 Hz, 1H), 6.02 (d, *J*=9.5 Hz, 1H), 4.21 (d, *J*=4.0 Hz, 1H), 3.87 (dd, *J*=7.5, 2.5 Hz, 1H), 3.69 (dd, *J*=8.0, 4.5 Hz, 1H), 3.65 (dd, *J*=5.5, 3.0 Hz, 1H), 0.91 (s, 9H), 0.12 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3, 143.2, 134.2, 128.6, 128.4, 126.0, 122.7, 79.6, 61.1, 57.3, 55.5, 25.6, 18.0, −3.9, −4.7; FABHRMS Calcd for $[C_{19}H_{26}O_4Si+Na]^+$: 369.1498. Found: 369.1505.

1.1.21. (5*S*)-5-Hydroxy-(6*S*)-6-((2*S*,3*R*)-3-phenyloxiranyl)-5,6-dihydro-pyran-2-one (2b). Compound **18** (30 mg, 0.087 mmol) was dissolved in 0.5 mL of THF and 130 μL (0.13 mmol) of a 1.0 M solution of TBAF was added to the solution at rt. The reaction was stirred for 0.5 h at rt. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (100% Et_2O) to give **2b**, 16.2 mg (0.07 mmol, 80%): R_f (100% Et_2O)=0.22; $[\alpha]^{21}_D$=+128.1 (*c* 0.16, CH_2Cl_2); IR (thin film, cm^{-1}) 3422, 2958, 2926, 2855, 1729, 1465, 1379, 1257, 1158, 1100, 1072, 1047; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.26 (m, 5H), 7.04 (dd, *J*=9.9, 6.0 Hz, 1H) 6.16 (d, *J*=9.6 Hz, 1H), 4.43 (dd, *J*=5.7, 2.7 Hz, 1H), 4.26 (dd, *J*=6.0, 2.7 Hz, 1H), 4.01 (d, *J*=1.8 Hz, 1H), 3.53 (dd, *J*=6.0, 2.1 Hz, 1H), 2.68 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 143.6, 135.5, 128.7, 128.6, 125.8, 123.4, 79.8, 60.8, 58.9, 57.9; FABHRMS Calcd for $[C_{13}H_{12}O_4+Na]^+$: 255.0633. Found: 255.0627.

1.1.22. (5*S*)-5-Hydroxy-(6*S*)-6-((2*S*,3*S*)-3-phenyloxiranyl)-5,6-dihydro-pyran-2-one (2d). Compound **19** (12 mg, 0.035 mmol) was dissolved in 0.3 mL of THF and 70 μL (0.07 mmol) of a 1.0 M solution of TBAF was added to the solution at rt. The reaction was stirred for 0.5 h at rt. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (100% Et_2O) to give **2d**, 6.2 mg (0.026 mmol, 80%): R_f (100% Et_2O)=0.25; $[\alpha]^{21}_D$=+44.3 (*c* 0.14, CH_2Cl_2); IR (thin film, cm^{-1}) 3413, 2924, 2880, 1732, 1372, 1250, 1099, 1054; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.32 (m, 5H), 6.96 (dd, *J*=9.9, 6.0 Hz, 1H), 6.06 (d, *J*=9.6 Hz, 1H), 4.37 (d, *J*=3.0 Hz, 1H), 4.32 (m, 1H), 3.76 (dd, *J*=9.6, 2.4 Hz, 1H), 3.71 (dd, *J*=9.9, 3.3 Hz, 1H), 2.24 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 143.3, 133.5, 128.6, 128.4, 126.3, 123.4, 75.9, 61.2, 57.6, 55.3; FABHRMS Calcd for $[C_{13}H_{12}O_4+H]^+$: 233.0814. Found: 233.0808.

1.1.23. (5*S*)-5-Hydroxy-(6*S*)-6-((2*R*,3*R*)-3-phenyloxiranyl)-5,6-dihydro-pyran-2-one (2a). Compound **20** (32 mg, 0.088 mmol) was dissolved in 0.9 mL of THF and 0.1 mL (0.1 mmol) of a 1.0 M solution of TBAF was added to the solution at rt. The reaction was stirred for 0.5 h at rt. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (100% Et_2O) to give **2a**, 17 mg (0.075 mmol, 85%): R_f (100% Et_2O)=0.26; $[\alpha]^{21}_D$=−6.0 (*c* 0.94, CH_2Cl_2); IR (thin film, cm^{-1}) 3431, 2950, 2853, 1716, 1497, 1455, 1377, 1262, 1107, 1089, 1050; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42–7.29 (m, 5H), 6.77 (dd, *J*=9.9, 6.0 Hz, 1H), 6.02 (d, *J*=9.6 Hz, 1H), 4.31 (d, *J*=4.2 Hz, 1H), 3.88 (dd, *J*=8.1, 2.7 Hz, 1H), 3.81 (dd, *J*=7.8, 4.2 Hz, 1H), 3.63 (dd, *J*=6.0, 3.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 143.3, 133.5, 128.6, 128.4, 126.3, 123.4, 75.9, 61.2, 57.6, 55.3; CIHRMS Calcd for $[C_{13}H_{12}O_4+NH_4]^+$: 250.1095. Found: 250.1095.

1.1.24. Isoaltholactone (1c). Compound **2b** (12.0 mg, 0.051 mmol) was dissolved in 0.5 mL of CH_2Cl_2 and a catalytic amount of CSA was added to the solution at rt. The reaction was stirred for 1.5 h at rt. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (100% Et_2O) to give **1c**, 11 mg (0.047 mmol, 93%): R_f (100% Et_2O)=0.33; $[\alpha]^{21}_D$=+26.1(*c* 0.56, EtOH); ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.31 (m, 5H), 6.90 (dd, *J*=10.0, 4.5 Hz, 1H), 6.23 (d, *J*=10.0 Hz, 1H), 5.08 (dd, *J*=5.5, 5.5 Hz, 1H), 4.89 (dd, *J*=5.5, 5.0 Hz, 1H), 4.79 (d, *J*=7.5 Hz, 1H), 4.29 (dd, *J*=7.5, 5.5 Hz, 1H), 2.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.06, 141.65, 138.35, 128.64, 128.30, 125.67, 122.96, 83.27, 78.51, 78.42, 67.67; FABHRMS Calcd for $[C_{13}H_{12}O_4+Na]^+$: 255.0633. Found: 255.0632.

1.1.25. 3-*epi*-Altholactone (1a). Compound **2d** (3.0 mg, 0.013 mmol) was dissolved in 0.15 mL of CH_2Cl_2 and a catalytic amount of CSA was added to the solution at rt. The reaction was stirred for 1.5 h at rt. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (100% Et_2O) to give **1a** and **1c** as a 1:1 mixture, 2.5 mg (0.011 mmol, 85%). *3-epi-Altholactone (**1a**)* and *Isoaltholactone (**1c**)* as a 1:1 mixture, 4.0 mg (0.017 mmol) was dissolved in 0.2 mL of CH_2Cl_2, 8 μL (0.07 mmol) of 2,6-lutidine, and 8 μL (0.03 mmol) of TBSOTf were added and stirred for 10 min. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (100% Et_2O) to give 1.5 mg (0.0065 mmol, 38%) of *3-epi-altholactone (**1a**)* and 2.0 mg (0.0058 mmol, 34%) of *3-tert-butyldimethylsilanyloxy isoaltholactone (**23**)*. *3-epi-Altholactone (**1a**)*: R_f (100% Et_2O)=0.36; $[\alpha]^{21}_D$=+30.7 (*c* 0.06, EtOH); IR (thin film, cm^{-1}) 3376, 2922, 2852, 1714, 1455, 1398, 1246, 1159, 1118, 1042; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40–7.32 (m, 5H), 6.88 (dd, *J*=10.0, 3.5 Hz, 1H), 6.15 (dd, *J*=10.0, 1.0 Hz, 1H), 5.24 (dd, *J*=8.0, 4.5 Hz, 1H), 5.10 (dd, *J*=4.5, 4.5 Hz, 1H), 4.81 (ddd, *J*=8.0, 3.5, 1.0 Hz, 1H), 4.56 (dd, *J*=4.5, 4.5 Hz, 1H), 1.82 (bs, 1H); ^{13}C NMR (75 MHz,

$CDCl_3$) δ 161.0, 141.5, 135.1, 128.5, 128.4, 126.8, 121.7, 80.8, 79.6, 73.8, 67.3; FABHRMS Calcd for $[C_{13}H_{12}O_4+Na]^+$: 255.0633. Found: 255.0634.

1.1.26. 3-*epi*-3-Benzoyl-altholactone (21) and 3-benzoyl isoaltholactone (22). *3-epi-Altholactone (**1a**)* and *isoaltholactone (**1b**)* as a 1:1 mixture, 6.0 mg (0.026 mmol) was dissolved in 0.3 mL of CH_2Cl_2,9.5 mg (0.078 mmol) of DMAP, and 9 μL (0.08 mmol) of benzoyl chloride were added and stirred for 6 h. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (30% EtOAc/hexanes) to give 3.5 mg (0.010 mmol, 38%) of *3-epi-3-benzoylaltholactone (**21**)* and 3.5 mg (0.01 mmol, 38%) of *3-benzoylisoaltholactone (**22**)*. *3-epi-3-Benzoylaltholactone (**21**)*: R_f (30% EtOAc/hexanes)=0.15; $[\alpha]^{21}_D$=+26.3(*c* 0.34, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12–8.10 (m, 1H), 7.50–7.46 (m, 2H), 7.34–7.19 (m, 5H), 6.98 (dd, *J*=10.0, 3.0 Hz, 1H), 6.20 (dd, *J*=10.0, 1.0 Hz, 1H), 5.99 (dd, *J*=5.5, 4.0 Hz, 1H), 5.55 (dd, *J*=8.0, 5.0 Hz, 1H), 5.27 (d, *J*=4.5 Hz, 1H), 4.97 (ddd, *J*=8.0, 3.5, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 160.2, 142.0, 134.6, 133.3, 129.4, 128.7, 128.4, 128.3, 128.1, 126.9, 121.2, 80.1, 78.1, 73.8, 67.4; FABHRMS Calcd for $[C_{20}H_{16}O_5+H]^+$: 337.1076. Found: 337.1085. *3-benzoylisoaltholactone (**22**)*: R_f (30% EtOAc/hexanes)=0.28; $[\alpha]^{21}_D$=−36.5 (*c* 0.15, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01–7.99 (m, 1H), 7.61–7.58 (m, 1H), 7.50–7.33 (m, 8H), 6.91 (dd, *J*=10.0, 3.5 Hz, 1H), 6.27 (dd, *J*=10.0, 1.0 Hz, 1H), 5.44 (dd, *J*=5.5, 5.5 Hz, 1H), 5.41 (dd, *J*=5.5, 5.5 Hz, 1H), 5.24 (d, *J*=5.0 Hz, 1H), 5.10 (ddd, *J*=5.5, 4.0, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 160.7, 142.0, 137.7, 133.7, 129.8, 128.8 (2C), 128.6 (2C), 125.6, 122.4, 81.6, 78.4, 76.2, 68.2; FABHRMS Calcd for $[C_{20}H_{16}O_5+H]^+$: 337.1076. Found: 337.1084.

1.1.27. Altholactone (1b) and 2-*epi*-altholactone (1d). Compound **2a** (6.0 mg, 0.026 mmol) was dissolved in 0.3 mL of CH_2Cl_2 and a catalytic amount of CSA was added to the solution at rt. The reaction was stirred for 12 h at rt. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (100% Et_2O) to give **1b** and **1d** as a 1:1 mixture, 5.0 mg (0.022 mmol, 80%). *Altholactone (**1b**)*: R_f (100% Et_2O)=0.29; $[\alpha]^{21}_D$=+162.8 (*c* 0.09, EtOH); IR (thin film, cm^{-1}) 3430, 2939, 2921, 2854, 1727, 1639, 1452, 1389, 1260, 1197, 1091, 1056; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39–7.30 (m, 5H), 7.00 (dd, *J*=9.9, 4.8 Hz, 1H), 6.24 (d, *J*=9.9 Hz, 1H), 4.95 (dd, *J*=5.4, 2.4 Hz, 1H), 4.75 (d, *J*=5.7 Hz, 1H), 4.66 (dd, *J*=5.4 Hz, 1H), 4.46(dd, *J*=5.7, 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 140.2, 138.0, 128.7, 128.4, 126.1, 123.7, 86.2, 86.0, 83.8, 68.2; CIHRMS Calcd for $[C_{13}H_{12}O_4+NH_4]^+$: 250.1079. Found: 250.1090. *2-epi-Altholactone (**1d**)*. R_f (100% Et_2O)=0.42; $[\alpha]^{21}_D$=+214.5 (*c* 0.11, EtOH); IR (thin film, cm^{-1}) 3430, 2956, 2925, 2857, 1731, 1450, 1390, 1248, 1095, 1044; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.33 (m, 5H), 7.01 (dd, *J*=9.6, 5.7 Hz, 1H), 6.22 (d, *J*=9.9 Hz, 1H), 5.37 (d, *J*=3.0 Hz, 1H), 5.10 (dd, *J*=4.5, 1.2 Hz, 1H), 4.86 (dd, *J*=5.4, 4.5 Hz, 1H), 4.52(bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 140.5, 134.7, 128.9, 128.7, 126.6, 123.1, 84.3, 83.5, 77.9, 68.2; CIHRMS Calcd for $[C_{13}H_{12}O_4+NH_4]^+$: 250.1079. Found: 250.1094.

1.1.28. 3-*epi*-3-Trifluoromethanesulfonyl-altholactone (24) and 3-trifluoromethanesulfonyl-isoaltholactone (25). *3-epi-Altholactone (**1a**)* and *isoaltholactone (**1b**)* as a 1:1 mixture, 4.0 mg (0.017 mmol) was dissolved in 0.2 mL of CH_2Cl_2, 20 μL (0.25 mmol) of pyridine, and 32 μL (0.19 mmol) of trifluoromethanesulfonic anhydride were added and stirred for 0.5 h. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (30% EtOAc/hexanes) to give 2.5 mg (0.007 mmol, 40%) of compound (**24**) and 2.5 mg (0.007 mmol, 40%) of compound (**25**). *3-epi-3-Trifluoromethanesulfonyl-altholactone (**24**)*: R_f (30% EtOAc/hexanes)=0.25; $[\alpha]^{21}_D$=+11.1 (*c* 0.35, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43–7.35 (m, 5H), 6.88 (dd, *J*=10.5, 3.0 Hz, 1H), 6.17 (dd, *J*=10.5, 2.0 Hz, 1H), 5.56 (dd, *J*=9.5, 5.0 Hz, 1H), 5.40 (dd, *J*=5.0, 3.0 Hz, 1H), 5.18 (d, *J*=3.0 Hz, 1H), 4.96 (ddd, *J*=9.0, 3.0, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 141.3, 132.1, 130.9, 129.4, 128.6, 127.2, 125.5, 120.8, 119.2, 116.7, 86.4, 79.4, 68.2, 66.6; FABHRMS Calcd for $[C_{14}H_{11}O_6SF_3+Na]^+$: 387.0126. Found: 387.0103. *3-Trifluoromethanesulfonyl-isoaltholactone (**25**)*: R_f (30% EtOAc/hexanes)=0.45; $[\alpha]^{21}_D$=−9.0 (*c* 0.20, CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45–7.38 (m, 5H), 6.85 (dd, *J*=10.5, 3.0 Hz, 1H), 6.22 (dd, *J*=10.0, 1.0 Hz, 1H), 5.28(dd, *J*=7.0, 5.5 Hz, 1H), 5.26 (d, *J*=4.5 Hz, 1H), 5.20 (d, *J*=5.5, 5.5 Hz, 1H), 5.09 (ddd, *J*=7.5, 3.5, 1.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 141.3, 135.5, 130.9, 129.4, 129.2, 128.8, 125.4, 122.4, 119.6, 110.0, 88.1, 81.5, 75.2, 67.8; FABHRMS Calcd for $[C_{14}H_{11}O_6SF_3+Na]^+$: 387.1026. Found: 387.0150.

1.1.29. 3-Forymloxy-altholactone (not shown). Compound **24** (7.0 mg, 0.019 mmol) was dissolved in 0.2 mL of DMF and cesium formate (10 mg, 0.58 mmol) was added to the solution at rt. The reaction was stirred for 4 h at rt. The reaction was quenched with 10 mL of Et_2O and 10 mL of sat aq $NaHCO_3$. The phases were separated and the aq layer was extracted (5×10 mL) with Et_2O. The organic fractions were combined, dried ($MgSO_4$), concentrated, and the crude product was purified by silica gel chromatography eluting with (100% Et_2O) to give *3-forymloxy-altholactone* (3 mg, 0.012 mmol) in a 60% yield: R_f (100% Et_2O)=0.26; $[\alpha]^{21}_D$=+50.4 (*c* 0.14, CH_2Cl_2); IR (thin film, cm^{-1}) 2958, 2926, 2854, 1732, 1716, 1651, 1463, 1455, 1246, 1150, 1101, 1069, 1025; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.36–7.31 (m, 5H), 7.05 (dd, *J*=10.0, 5.5 Hz, 1H), 6.30 (d, *J*=10.0 Hz, 1H), 5.50 (d, *J*=3.5 Hz, 1H), 5.00 (d, *J*=4.0 Hz, 1H), 4.99 (dd, *J*=4.0, 1.0 Hz, 1H), 4.64 (dd, *J*=5.5, 4.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.9, 159.0, 139.0, 130.9, 128.7 (2C), 126.2, 124.8, 85.9, 83.8, 83.2, 69.1; CIHRMS Calcd for $[C_{14}H_{12}O_5+NH_4]^+$: 278.1028. Found: 278.1037.

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References

1. (a) Blazquez, M. A.; Bermejo, A.; Zafra-Polo, M. C.; Cortes, D. *Phytochem. Anal.* **1999**, *10*, 161–170. (b) Bermejo, A.; Blazquez, M. A.; Rao, K. S.; Cortes, D. *Phytochem. Anal.* **1999**, *10*, 127–131. (c) Yasui, K.; Tamura, Y.; Nakatani, T.; Kawada, K.; Ohtani, M. *J. Org. Chem.* **1995**, *60*, 7567–7574 and references cited therein. (d) Fang, X.-P.; Anderson, J. E.; Chang, C.-J.; McLaughlin, J. L.; Fanwick, P. E. *J. Nat. Prod.* **1991**, *54*, 1034. (e) Argoudelis, A. D.; Zieserl, J. F. *Tetrahedron Lett.* **1969**, *18*, (1966). (f) For a review of 5,6-dihydro-2*H*-pyran-2-ones, see: Davies-Coleman, M. T.; Rivett, D. E. A. *Progress in the Chemistry of Organic Natural Products*, Herz, W., Grisebach, H., Kirby, G. W., Tamm, Ch., Eds.; Springer: New York, 1989; Vol. 55, pp 1–35.
2. (a) Schlessing, R. H.; Gillman, K. W. *Tetrahedron Lett.* **1999**, *40*, 1257–1260. (b) Tsubuki, M.; Kanai, K.; Nagase, H.; Honda, T. *Tetrahedron* **1999**, *55*, 2493. (c) Chen, W.-P.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 103–105. (d) Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3125–3126. (e) Yang, Z.-C.; Jiang, X.-B.; Wang, Z.-M.; Zhou, W.-S. *J. Chem. Soc., Perkin Trans. 1* **1997**, 317–321. (f) Gomez, A. M.; Lopez de Uralde, B.; Valverde, S.; Lopez, J. C. *J. Chem. Soc., Chem. Commun.* **1997**, 1647. (g) Honda, T.; Sano, N.; Kanai, K. *Heterocycles* **1995**, *41*, 425–429. (h) Yang, Z.-C.; Zhou, W.-S. *Tetrahedron Lett.* **1995**, *36*, 5617–5618. (i) Masaki, Y.; Imaeda, T.; Oda, H.; Itoh, A.; Shiro, M. *Chem. Lett.* **1992**, 1209–1212. (j) For a review see: Ogliaruso, M. A.; Wolfe, J. F. In *Synthesis of Lactones and Lactams*, Patai, S., Rappoport, Z., Eds.; Wiley: New York, 1993; pp 3–131 271–396.
3. Balachari, D.; O'Doherty, G. A. *Org. Lett.* **2000**, *2*, 863–866.
4. Loder, J. W.; Nearn, R. H. *Heterocycles* **1977**, *7*, 113.
5. (a) Gesson, J.-P.; Jacquesy, J.-C.; Mondon, M. *Tetrahedron Lett.* **1987**, *28*, 3945–3948. (b) Gesson, J.-P.; Jacquesy, J.-C.; Mondon, M. *Tetrahedron Lett.* **1987**, *28*, 3949–3952. (c) Gesson, J.-P.; Jacquesy, J.-C.; Mondon, M. *Tetrahedron* **1989**, *45*, 2627–2640.
6. (a) Gillhouley, J. G.; Shing, T. K. M. *J. Chem. Soc., Chem. Commun.* **1988**, 976–977. (b) Shing, T. K. M.; Gillhouley, J. G. *Tetrahedron* **1994**, *50*, 8685–8698. (c) Shing, T. K. M.; Tsui, H.-C.; Zhou, Z.-H. *J. Org. Chem.* **1995**, *60*, 3121–3130.
7. Ueno, Y.; Tadano, K.; Ogawa, S.; McLaughlin, J. L.; Alkofahi, A. *Bull. Chem. Soc. Jpn* **1989**, *62*, 2328–2337.
8. Kang, S. H.; Kim, W. J. *Tetrahedron Lett.* **1989**, *30*, 5915–5918.
9. (a) Tsubuki, M.; Kanai, K.; Honda, T. *Synlett* **1993**, 653–655. (b) Tsubuki, M.; Kanai, K.; Nagase, H.; Honda, T. *Tetrahedron* **1999**, *55*, 2493–2514.
10. Somfai, P. *Tetrahedron* **1994**, *50*, 11315–11320.
11. (a) Mukai, C.; Hirai, S.; Kim, I. J.; Hanaoka, M. *Tetrahedron Lett.* **1996**, *37*, 5389–5392. (b) Mukai, C.; Hirai, S.; Hanaoka, M. *J. Org. Chem.* **1997**, *62*, 6619–6626.
12. (a) Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982–2983. (b) Harris, J. M.; Keranen, M. D.; Nguyen, H.; Young, V. G.; O'Doherty, G. A. *Carbohydr. Res.* **2000**, *328*, 17–36.
13. Harris, J. M.; O'Doherty, G. A. *Tetrahedron Lett.* **2000**, *41*, 183–187.
14. (a) Grapsas, I.; Couladouros, E. A.; Georgiadis, M. P. *Pol. J. Chem.* **1990**, *64*, 823. (b) Georgiadis, M. P.; Couladoros, E. A. *J. Org. Chem.* **1986**, *51*, 2725–2727.
15. Achmatowicz, O.; Bielski, R. *Carbohydr. Res.* **1977**, *55*, 165.
16. Luche, J.-L. *J. Am. Chem. Soc.* **1978**, *110*, 2226.
17. All new compounds were identified and characterized by ^{1}H NMR, ^{13}C NMR, FTIR, HRMS, and EA analysis.
18. Enantiomeric excesses were determined by ^{1}H NMR and ^{19}F NMR of the mosher ester derivative.
19. Even after long reaction times (>24 h) only the primary TBS group was cleaved.
20. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, 26–28.
21. The *cis*/*trans* selectivity of the Wittig reaction decreased to 4:1 at 0°C and to 2:1 at room temperature.
22. Barrett, A. G. M.; Hamprecht, D.; Ohkubo, M. *J. Org. Chem.* **1997**, *62*, 9376–9378.
23. Colgate, S. M.; Din, L. B.; Latiff, A.; Matsalleh, K.; Samudin, M. W.; Skelton, B. W.; Tadano, K. I.; White, A. H.; Zakria, Z. *Phytochemistry* **1990**, *29*, 1701–1704.
24. Hawryluk, N. A.; Snider, B. B. *J. Org. Chem.* **2000**, *65*, 8379–8380.
25. Grieco, P. A.; Henry, K. J.; Nunes, J. J.; Matt, J. E. *J. Chem. Soc., Chem. Commun.* **1992**, 368–370.
26. Our spectral data for synthetic 1a-d and 3a (^{1}H NMR, ^{13}C NMR, FTIR, HRMS, and optical rotation) matched the data for the isolated material.