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Use of a palladium(II)-catalyzed oxidative kinetic resolution in synthetic efforts toward bielschowskysin

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ABSTRACT

Progress toward the cyclobutane core of bielshowskysin is reported. The core was thought to arise from a cyclopropane intermediate via a furan-mediated cyclopropane fragmentation, followed by a 1,4-Michael addition. The synthesis of the cyclopropane intermediate utilizes a Suzuki coupling reaction, an esterification with 2-diazoacetoacetic acid, and a copper catalyzed cyclopropanation. An alcohol intermediate within the synthetic route was obtained in high enantiopurity via a highly selective palladium(II)-catalyzed oxidative kinetic resolution (OKR).

1. Introduction

In 2003, several novel natural products were isolated from the Caribbean gorgonian octocoral *Pseudopterogorgia kallos*. The structure of one of these compounds, bielschowskysin (**1**), eluded characterization until an X-ray crystal structure was obtained approximately one year later.[1] Bielschowskysin belongs to the *pseudopterane* sub-class of molecules, and is one of several structurally and biosynthetically related diterpenes (Fig. 1).[2] Furthermore, bielschowskysin has been identified as a potent inhibitor of EKVX lung cancer cells (GI_{50}=10 nM).

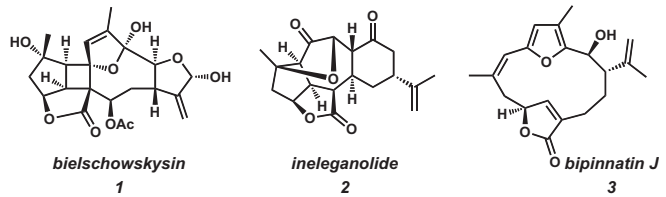

Fig. 1. Bielschowskysin and related natural products.

A characteristic feature of these molecules is a cis-fused[5,5]oxabicycle, as well as a dihydrofuran unit that is sometimes disguised as a 1,4 diketone moiety.[3] Bielschowskysin contains a polycyclic ring system bearing eleven stereocenters, one of which is a quaternary stereocenter contained in a hexasubstituted cyclobutane ring that is also fused to a substituted oxocane ring, resulting in a highly strained cage-like structure.[4] A proposed biosynthesis by Trauner theorizes that the bielschowskysin core arises from a simpler *cembranoid* natural product, bipinnatin J (**3**, Fig. 1), via olefin hydration, followed by a [2+2] cycloaddition to form the cyclobutane core.[5]

Several partial syntheses of bielschowskysin's cyclobutane core have been reported;[6] yet only one of these reports includes the stereogenic quaternary center contained in the cyclobutane ring.[6d] Toward planning an initial synthetic route to bielschowskysin (**3**), a suitable model system was designed to investigate the key formation of the cyclobutane core as well as the quaternary stereocenter. Hence, our synthetic target was cyclobutane **4** (Scheme 1). We predicated our synthetic strategy upon the formation of cyclobutane **4** via a Lewis acid-mediated cyclopropane fragmentation of ketone **6**, leading to intermediate **5**, followed by a 1,4-Michael addition (Scheme 1). Ihara has shown that a domino sequence involving a Michael addition followed by an aldol reaction providing strained bicyclo[3.2.0]heptane systems is achievable.[7] We envisioned cyclopropane **6** arising from α-diazo-β-ketoester **7** by a cyclopropanation reaction using either a copper or rhodium

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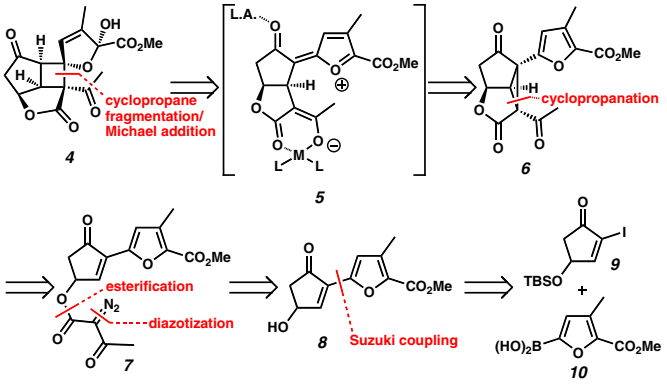
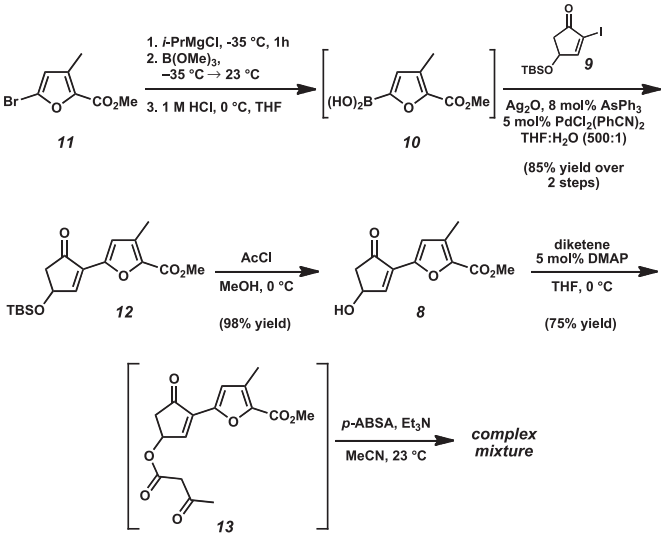
catalyst. In turn, α-diazo-β-ketoester **7** could be obtained from allylic alcohol **8** via esterification and diazotization. The latter compound, alcohol **8**, can be prepared via Suzuki coupling between iodide **9** and boronic acid **10**. Moreover, we postulated that allylic alcohol **8** could be used as a branch point for an enantioselective approach to this molecule. We anticipated that the stereocenter in alcohol **8** would provide a basis for the application of a substrate-focused palladium(II)-catalyzed oxidative kinetic resolution, developed independently by the Sigman and Stoltz laboratories.[8,9] Accomplishing the latter would provide access to an enantioselective synthesis of cyclopropane **6**, as well as eventually bielschowskysin (**1**).



Scheme 1. Retrosynthetic analysis of cyclobutane **4**.

2. Results and discussion

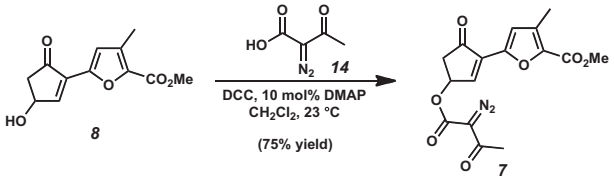
The synthesis began with furan **11**,[10] which underwent magnesium–halogen exchange using conditions developed by Knochel,[11] followed by a sequential quench of trimethyl borate and 1 M HCl to furnish boronic acid **10** in 85% yield (Scheme 2). Coupling of iodoenone **9** with boronic acid **10** under similar conditions reported by Johnson provided compound **12** in excellent yield.[12,13] At this stage, cleavage of the TBS group under acidic conditions provided allylic alcohol **8** in 98% yield. Exposure of allylic alcohol **8** to diketene and a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine (DMAP) afforded unstable β-ketoester **13**. Unfortunately, immediate treatment of β-ketoester **13** with *p*-ABSA and Et_3N did not yield the desired diazo product; instead, a complex mixture of



Scheme 2. Attempted synthesis of α-diazo-β-ketoester **7**.

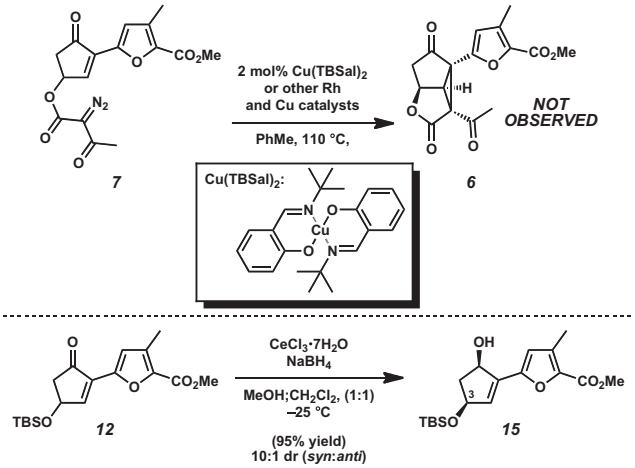
byproducts, likely a result of the nucleophilic β-ketoester undergoing a Michael addition into the enone, was obtained. After several attempts to form α-diazo-β-ketoester **7** from intermediate **13** under neutral diazo transfer conditions failed to provide the desired product, we decided to move in a different direction.

At this stage, we began to postulate the feasibility of attaching the β-ketoester and the diazo group in a single operation. This thought, coupled with the observation that the conditions to form β-ketoester **13** (diketene/cat. DMAP/THF) are essentially neutral, led us to attempt a coupling between alcohol **8** and a novel reagent, 2-diazoacetoacetic acid (**14**, Scheme 3). This reagent would not only reduce the synthesis by one step, but also prevent any undesired Michael reactions from occurring by having the diazo moiety remove the nucleophilicity of the β-ketoester. Gratifyingly, the synthesis of 2-diazoacetoacetic acid (**14**) was accomplished in a straightforward manner,[14] and it was found that using acid **14** with DCC and a catalytic amount of DMAP provided α-diazo-β-ketoester **7** in 75% yield.[14]



Scheme 3. Synthesis of α-diazo-β-ketoester **7** using 2-diazoacetoacetic acid (**14**).

With α-diazo-β-ketoester **7** now synthesized, we then explored numerous Cu and Rh catalysts known to effect cyclopropanation, including $Cu(TBSal)_2$, Cu bronze, $Rh_2(oct)_4$, and $Cu(acac)_2$. Unfortunately, formation of cyclopropane **6** was never observed using these catalysts (Scheme 4).[15] We hypothesized that the enone functionality contributed to a withdrawal of electron density from the olefin, and thus inhibited cyclopropanation.



Scheme 4. Initial cyclopropanation results and synthesis of alcohol **15**.

As a result, we elected to modify the synthesis by reducing the ketone functionality in enone **12** (Scheme 4) to alcohol **15**. We theorized that this would increase the electron density and the corresponding nucleophilicity of the olefin to facilitate cyclopropanation. Furthermore, we have previously shown 2-aryl cyclic allylic alcohols to be exceptional substrates in our palladium(II)-catalyzed oxidative kinetic resolution.[9d] Therefore, diastereoselective 1,2-reduction of the enone functionality in compound **12** provided the necessary substrate (**15**) with which to explore the palladium(II)-catalyzed oxidative kinetic resolution and allow us to establish the absolute stereochemistry at C(3).

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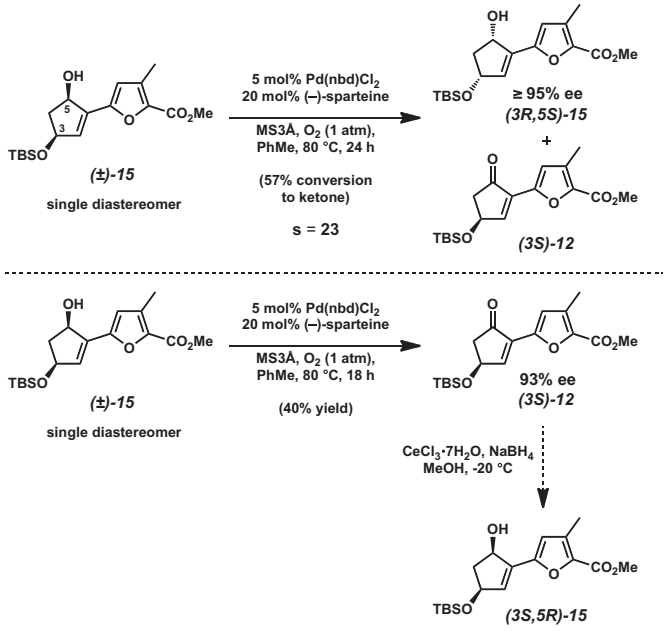
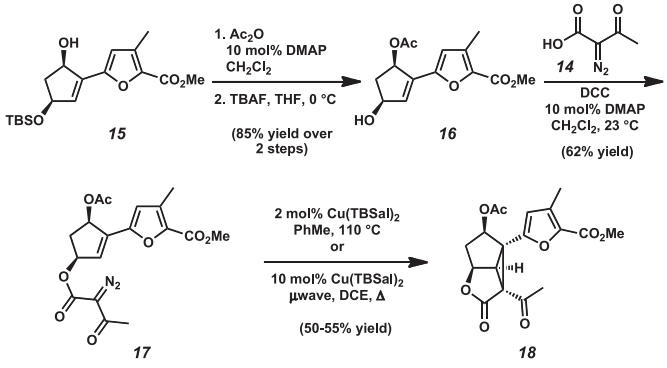
To that end, treatment of racemic alcohol **15** under conditions developed for the palladium(II)-catalyzed oxidative kinetic resolution afforded enantioenriched (3*R*,5*S*)-alcohol **15** in ≥95% ee and high selectivity (*s*=23, Scheme 5), as well as (3*S*)-ketone **12** in 57% conversion after 24 h.[16] Furthermore, in a separate run it was found that after 18 h, (3*S*)-ketone **12** was obtained in 40% yield and 93% ee. With these results, if (3*S*)-ketone **12** was subjected to the diastereoselective Luche reduction shown in Scheme 4, (3*S*,5*R*)-alcohol **15** would be obtained, and thus provide access to either enantiomer of alcohol **15** in high enantioselectivity (Scheme 5). Since the absolute configuration of bielschowskysin is unknown, accessing both enantiomers of alcohol **15** in this fashion is important, as it provides a route to potentially synthesize either enantiomer of the natural product.



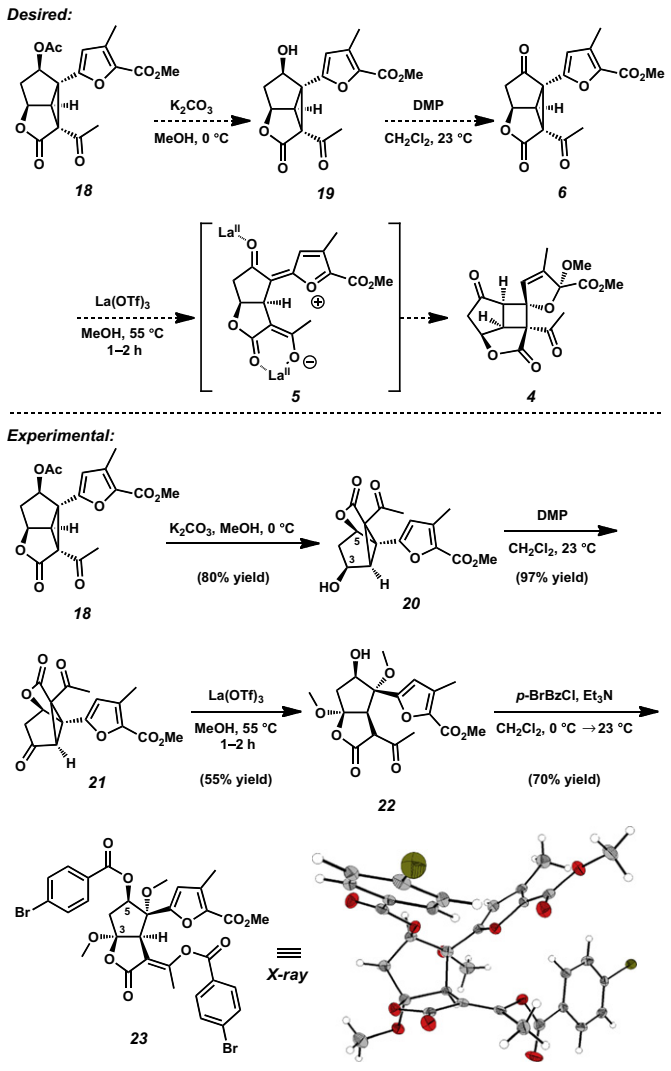
Scheme 5. Results of Pd(II)-catalyzed OKR.

Given the success of the palladium(II)-catalyzed oxidative kinetic resolution, our efforts shifted to the synthesis of cyclopropane **6**, and subsequent investigations into the formation of cyclobutane **4**. Beginning with furan **15**, acetate protection of the alcohol and subsequent cleavage of the silyl ether unveiled allylic alcohol **16** in 85% overall yield (Scheme 6). The latter compound underwent coupling with 2-diazoacetoacetic acid (**14**) to provide α-diazo-β-ketoester **17** in 62% yield. Initially, attempts to form the cyclopropane ring using several rhodium and copper catalysts did not provide any of the desired product. Gratifyingly, formation of the cyclopropane was accomplished using 2 mol % $Cu(TBSal)_2$ in either toluene at reflux temperature or heating in a microwave using 1,2-dichloroethane as solvent to provide cyclopropane **18** in 50–55% yield.[17] This result is consistent with our hypothesis that the olefin in enone **7** is simply too electron deficient to undergo cyclopropanation.



Scheme 6. Formation of cyclopropane intermediate **18**.

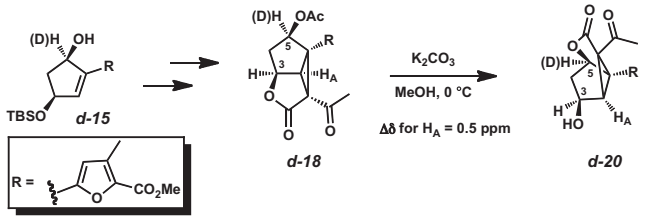
Although the synthesis of cyclopropane **18** was a significant accomplishment, this intermediate still needed to be elaborated to ketone **6**. Initially, it was thought that cyclopropane **18** would undergo acetate cleavage using K_2CO_3/MeOH conditions to provide alcohol **19**, followed by Dess–Martin periodinane oxidation to arrive at ketone **6** (Scheme 7, top). We hoped that exposing ketone **6** to a Lewis acid would lead to a furan-assisted fragmentation of the cyclopropane ring to provide zwitterionic intermediate **5**, followed by a Michael addition to afford the highly functionalized cyclobutane **4**. Thus, we treated acetate **18** with a sequence of reagents consisting of K_2CO_3/MeOH (to cleave the acetate group), DMP (to oxidize the resulting alcohol to the ketone), and $La(OTf)_3$ in MeOH at 55 °C (to effect the desired skeletal rearrangement). Through this sequence, a single major product was obtained in each step (first an alcohol (**20**), then a ketone (**21**), then a rearranged product (**22**)). Although this rearranged compound had some of the characteristics of the desired product, it clearly was not cyclobutane **4**, as it was unmistakably an alcohol (determined by IR spectroscopy). Since we were unable to confirm the complete structure of the final product of this sequence via routine spectroscopic methods (i.e., IR and NMR), we chose to esterify compound **22** to provide ester **23**,



Scheme 7. Synthesis of unexpected β-ketoester **22**.

which enabled us to grow crystals suitable for analysis by X-ray crystallography.[18] To our surprise, the X-ray data provided an unexpected structure from the sequence, β-ketoester **22**. Upon examination of the connectivity of β-ketoester **22**, it was apparent that the oxidation states at C(3) and C(5) were opposite to those of ketone **6**. In light of the data, we suspected that an undesired translactonization had occurred during acetate removal, and that the position of the alcohol in intermediate **20** was at C(3) rather than C(5).

To confirm this undesired rearrangement, we partially incorporated deuterium at C(5) using a 1:1 mixture of $NaBH_4$:$NaBD_4$ in the Luche reduction that produced alcohol *d*-**15**, allowing us to follow the chemical shifts of the protons on both C(3) and C(5) during the course of acetate removal (Scheme 8). As anticipated, the C(3) proton in intermediate *d*-**20** exhibited a slight upfield shift, while the C(5) proton underwent a downfield shift in the ^{1}H NMR. Interestingly, cyclopropyl proton H_A exhibits a change in resonance by 0.50 ppm that we attribute to conformational changes that result from transesterification. These results helped to verify that the translactonization reaction does in fact occur during acetate removal.



Scheme 8. Verifying the translactonization by partial deuterium labeling.

In an effort to circumvent the translactonization reaction, we synthesized a variety of donor–acceptor cyclopropanes similar to cyclopropane **18**, differing only in the hydroxyl protecting group at C(5) (Fig. 2).[19,20] We postulated that these protecting groups may be removed under conditions that suppress the formation of alcohol **20**. Unfortunately, all attempts to deprotect compounds **24**–**28** in Fig. 2 led solely to undesired alcohol **20**. This result led us to conclude that the undesired lactone (**20**) is likely the thermodynamic product.[21]

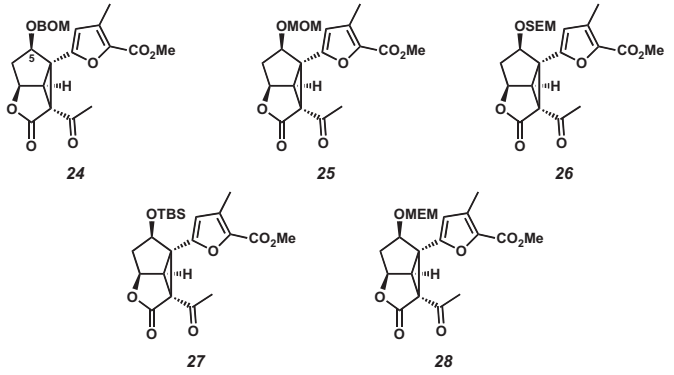
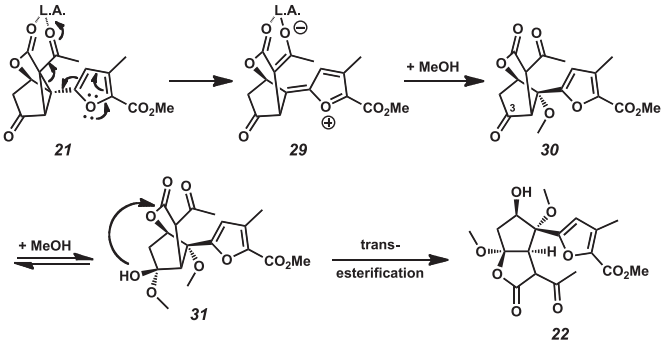


Fig. 2. Donor–acceptor cyclopropanes with various protecting groups for the C(5) alcohol.

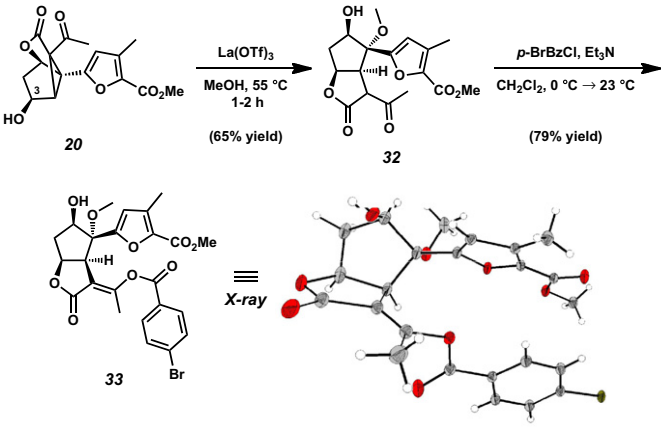
Further analysis can be made from the Lewis acid-mediated fragmentation reaction of cyclopropyl ketone **21** to provide unexpected alcohol **22**. Beginning with ketone **21** (Scheme 9), it is thought that Lewis acidic activation weakens the cyclopropane ring to allow the furan ring to assist in fragmentation to form an enolate and an extended oxocarbenium ion in intermediate **29**, both of which are quenched, respectively, by the net addition of methanol to provide ketone **30**. Thus, fragmentation of the cyclopropane ring



Scheme 9. Proposed mechanism of the formation of bicycle **22**.

occurred as anticipated; however, the addition of methanol preserved the aromaticity in the furan ring rather than undergoing a 1,2-addition into the oxocarbenium ion. Rearomatization is likely the driving force for the observed chemoselectivity in the methanol addition. Furthermore, under these conditions, an additional molecule of methanol can add into ketone **30** from the less-hindered α-face to form a hemiketal at C(3). Intermediate **31** can now undergo transesterification to produce alcohol **22**. Notably, formation of the hemiketal at C(3) can occur at any point in the reaction; however, transesterification to generate the fused lactone is not favorable until the cyclopropane ring undergoes fragmentation.

To examine this hypothesis, we subjected alcohol **20** to identical Lewis acidic conditions that resulted in the formation of alcohol **32** in 65% yield as a single diastereomer (Scheme 10). Alcohol **32** can undergo subsequent functionalization to provide compound **33**, allowing for suitable X-ray analysis.[22] We initially believed that the hemiketal in intermediate **31** might force the alcohol into a pseudoaxial position and promote transesterification. However, by forming alcohol **32** without the ability for ketalization, we have shown that transesterification is facile once the cyclopropane ring has fragmented, regardless of the C(3) oxidation state.



Scheme 10. Formation and confirmation of alcohol **32**.

3. Conclusion

Although the cyclopropane route did not achieve its ultimate goal in synthesizing the cyclobutane ring of bielschowskysin, several interesting aspects of our research can be extracted. First, we have successfully implemented the palladium(II)-catalyzed oxidative kinetic resolution early in the synthesis to provide alcohol **15** in ≥95% ee and 43% yield. This method allows for rapid access to either enantiomer of allylic alcohol **15**, an important intermediate in synthesizing advanced compounds within our synthetic efforts.

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Second, we synthesized and used 2-diazoacetoacetic acid (**14**) to provide α-diazo-β-ketoester **7**, which was unattainable through known methods. Finally, we discovered two interesting transesterification processes that led to a highly functionalized, fused bicyclic scaffold. By studying these separate transesterifications and understanding why they occur, we have gained an understanding of the reactivity of these molecules, and anticipate that continued efforts will pave the way for the formation of the cyclobutane core of bielschowskysin. Current efforts are focused on manipulating intermediate **32** into cyclobutane **4**, as well as synthesizing the macrocyclic portion of bielschowskysin.

4. Experimental section

4.1. General

Unless otherwise stated, reactions were performed at ambient temperature (typically 20–22 °C) in flame-dried glassware under an argon or nitrogen atmosphere using dry solvents. Solvents were dried by passage through an activated alumina column under argon. Et_3N, $^iPr_2NH$, $^iPr_2NEt$, and pyridine were freshly distilled from CaH_2. All other commercially obtained reagents were used as received. Reaction temperatures were controlled by an IKAmag temperature modulator. All microwave reactions were performed with a Biotage Initiator 2.5 microwave. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F_{254} precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, $KMnO_4$, or CAM staining. ICN silica gel (particle size 0.032–0.063 mm) was used for flash chromatography. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz, respectively), or a Varian Inova 500 (at 500 MHz and 125 MHz, respectively) and are reported relative to solvent for ^1H NMR ($CHCl_3$=7.27 ppm, C_6H_6=7.16 ppm, CH_2Cl_2=5.30 ppm, DMSO=2.51 ppm) and ^{13}C NMR ($CDCl_3$=77.0 ppm, C_6D_6=128.4 ppm). Data for ^1H NMR spectra are reported as follows: chemical shift (δ parts per million) (multiplicity, coupling constant (hertz), integration). Multiplicities are reported as follows: s=singlet, d=doublet, t=triplet, q=quartet, dt=doublet of triplets, td=triplet of doublets, dd=doublet of doublets, m=multiplet, comp. m=complex multiplet, app.=apparent, br s=broad singlet. IR spectra were recorded on a Perkin Elmer BX-11 FT-IR spectrometer and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra were obtained from the California Institute of Technology Mass Spectral Facility. Crystallographic analyzes were performed at the California Institute of Technology Beckman Institute X-ray Crystallography Laboratory. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, from the CCDC by quoting the publication citation and the deposition number.

4.2. Methyl-5-(3-((*tert*-butyldimethylsilyl)oxy)-5-oxocyclopent-1-en-1-yl)-3-methylfuran-2-carboxylate (12)

To a solution of furan **11** (609 mg, 2.78 mmol, 1.00 equiv) in THF (15 mL) at −35 °C, was added a 1.84 M solution (THF) of ^{i}PrMgCl (1.96 mL, 3.61 mmol, 1.30 equiv). The reaction was stirred for 45 min and the temperature was maintained between −40 and −30 °C. At this stage, trimethyl borate (1.24 mL, 11.1 mmol, 4.00 equiv) was added rapidly at −30 °C, and the reaction was allowed to warm to ambient temperature and stir overnight. The reaction was cooled to 0 °C, 1 M HCl (aq) was added, and the mixture stirred for 30 min. The reaction was diluted with EtOAc and H_2O, and the layers were separated. The aqueous layer was then extracted 2× with EtOAc. The organic layers were combined, transferred into an Erlenmeyer flask with stirring, and satd K_2CO_3 (aq) was carefully added until the aqueous layer remained basic. The basic aqueous layer was then acidified using 1 M HCl (aq), and then extracted 5× with EtOAc. The latter batch of EtOAc was washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to afford boronic acid **10** (375 mg, 73%) as a light-brown solid. This compound was used directly in the following Suzuki coupling reaction.

To a solution of vinyl iodide **9** (87.0 mg, 0.260 mmol, 1.00 equiv), boronic acid **10** (71.0 mg, 0.390 mmol, 1.50 equiv), Ag_2O (180 mg, 0.770 mmol, 3.00 equiv), and Ph_3As (8.00 mg, 0.0260 mmol, 0.100 equiv) in THF (1.30 mL) was added $PdCl_2(PhCN)_2$ (5.00 mg, 0.0130 mmol, 0.0500 equiv) and H_2O (50.0 μL). The reaction was stirred until complete consumption of vinyl iodide **9**, as indicated by TLC (ca. 1.5 h), and filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography using 3:97→5:95 EtOAc/hexanes to afford furan **12** as a white solid (74 mg, 80%). R_f 0.15 (90:10 hexanes/EtOAc, UV); ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J=2.7 Hz, 1H), 7.03 (s, 1H), 5.03 (m, 1H), 3.90 (s, 3H), 2.88 (dd, J=5.9, 18.3 Hz, 1H), 2.42 (dd, J=2.2, 18.6 Hz, 1H), 2.34 (s, 3H), 0.91 (s, 9H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 160.1, 156.0, 147.4, 140.0, 133.7, 132.6, 116.1, 68.9, 51.8, 45.9, 25.8, 18.3, 11.5, −4.8; IR (film) 3133, 2949, 2928, 2891, 2857, 1721, 1703, 1594, 1509, 1448 cm^{-1}; HRMS (FAB^+) calcd for $[C_{18}H_{26}SiO_5]^+$: m/z 350.1550, found 350.1542.

4.3. Methyl-5-(3-hydroxy-5-oxocyclopent-1-en-1-yl)-3-methylfuran-2-carboxylate (8)

To a solution of acetyl chloride (50.5 μL, 0.710 mmol, 5.00 equiv) in MeOH (570 μL) at 0 °C, was added enone **12** (52.5 mg, 0.150 mmol, 1.00 equiv) in one portion. Enone **12** dissolved slowly over 20–30 min at 0 °C, and once completely in solution, the reaction stirred for 45 min at 0 °C. The reaction was then diluted with brine and EtOAc, and these layers were separated. The aqueous layer was extracted 2× with EtOAc. The organic layers were combined, washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. This semi-solid was diluted with toluene, and then concentrated under vacuum (repeated 3×). Upon final concentration in vacuo, alcohol **8** was obtained as a white solid (35.3 mg, 99%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J=2.9 Hz, 1H), 7.02 (s, 1H), 5.21 (br, 1H), 3.90 (s, 3H), 2.96 (dd, J=6.1, 18.8 Hz, 1H), 2.71 (d, J=5.40 Hz, 1H), 2.49 (dd, J=2.2, 18.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.8, 160.0, 154.9, 147.1, 139.9, 134.1, 132.4, 116.1, 68.3, 51.7, 45.2, 11.6; IR (film) 3447, 2920, 2850, 1716, 1506, 1440, 1405, 1295, 1167, 1102 cm^{-1}; HRMS (FAB^+) calcd for $[C_{12}H_{13}O_5]^+$: m/z 237.0763, found 237.0763.

4.4. Methyl-5-(3-((2-diazo-3-oxobutanoyl)oxy)-5-oxocyclopent-1-en-1-yl)-3-methylfuran-2-carboxylate (7)

To a solution of alcohol **8** (71.0 mg, 0.300 mmol, 1.00 equiv), acid **14** (92.1 mg, 0.720 mmol, 2.40 equiv), and DMAP (3.67 mg, 0.0300 mmol, 0.100 equiv) in CH_2Cl_2 (2.00 mL) at 23 °C, was added DCC (206 mg, 1.00 mmol, 2.0 equiv) in one portion. After the addition of DCC, the reaction was heated to 40 °C for 90 min. The reaction was allowed to cool to ambient temperature, filtered through a plug of Celite (Et_2O eluent), and the resulting filtrate was partitioned between H_2O and Et_2O. The aqueous layer was extracted 2× with Et_2O. The organic extracts were combined, washed once with H_2O, and then once with brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The product was purified by flash chromatography using 25:75 EtOAc/hexanes to afford compound **7** as a light-yellow solid (78 mg, 75% yield). ^1H NMR (500 MHz, C_6D_6) δ 7.30 (s, 1H), 7.23 (s, 1H), 5.24 (m, 1H), 3.46 (s, 3H), 2.33 (dd, J=6.6, 18.6 Hz, 1H), 2.24 (s, 3H), 2.18 (s, 3H), 1.90 (d, J=18.6 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.3, 188.6, 160.8, 159.9, 149.1, 147.3, 141.4, 136.4, 132.7, 117.5, 71.2, 51.5, 42.0, 28.4,

11.8; IR (film) 2954, 2145, 1715, 1660, 1366, 1312, 1155, 1062 cm^{-1}; HRMS (FAB^+) calcd for $[C_{16}H_{14}N_2O_7]^+$: *m*/*z* 346.0801; found, 346.0817.

4.5. Methyl-5-(3-((*tert*-butyldimethylsilyl)oxy)-5-hydroxycyclopent-1-en-1-yl)-3-methylfuran-2-carboxylate (15)

To a solution of furan **12** (100 mg, 0.290 mmol, 1.00 equiv) and $CeCl_3{\cdot}7H_2O$ (430 mg, 1.10 mmol, 4.00 equiv) in $MeOH/CH_2Cl_2$ (4.90 mL, 1:1) at −25 °C, was added sodium borohydride (43.0 mg, 1.10 mmol, 4.00 equiv) portionwise while maintaining the reaction between −25 and −20 °C. Upon consumption of the ketone as visualized by TLC (ca. 30 min), the reaction was diluted with EtOAc and H_2O. The solution was allowed to warm to ambient temperature and the layers were separated. The aqueous layer was extracted 3× with EtOAc, and the organic layers were combined and washed with brine. The EtOAc layer was dried with Na_2SO_4, filtered, and concentrated in vacuo to provide allylic alcohol **15** as a yellow oil (96 mg, 95%). R_f=0.20 (20:80 EtOAc/hexanes, UV); ^1H NMR (500 MHz, $CDCl_3$) δ 6.58 (s, 1H), 6.39 (s, 1H), 4.84 (m, 1H), 4.79 (m, 1H), 3.91 (s, 3H), 2.76 (dt, *J*=6.9, 14.2 Hz, 1H), 2.36 (s, 3H), 1.98 (d, *J*=9.3 Hz, 1H), 1.77 (d, *J*=14.2 Hz, 1H), 0.92 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.0, 151.7, 139.5, 136.2, 133.0, 132.6, 113.7, 74.8, 74.2, 51.5, 44.7, 25.8, 18.1, 11.6, −4.6, −4.7; IR (film) 3420, 2954, 2930, 2857, 1711, 1440, 1298, 1101 cm^{-1}; HRMS (FAB^+) calcd for $[C_{18}H_{27}O_5Si]^+$: *m*/*z* 351.1628; found 351.1632.

4.6. Methyl-5-((3*R*,5*S*)-3-((*tert*-butyldimethylsilyl)oxy)-5-hydroxycyclopent-1-en-1-yl)-3-methylfuran-2-carboxylate (3*R*,5*S*-15)

A 10 mL Schlenk tube equipped with a magnetic stir bar was charged with powdered molecular sieves (3 Å MS, 150 mg) and flame-dried under vacuum. After cooling under dry N_2, $Pd(nbd)Cl_2$ (0.380 mg, 1.42 μmol, 0.0500 equiv) was added, followed by toluene (285 μL). To this yellow suspension was added (−)-sparteine (1.33 mg, 5.67 μmol, 0.200 equiv), and the top of the Schlenk tube was then fitted with an O_2 balloon. The reaction was purged under vacuum and replaced with O_2, and this process was repeated 4×'s. The light-yellow suspension was stirred at ambient temperature for 10 min, then heated to 80 °C for an additional 10 min. The reaction mixture darkened to an orange suspension. Upon completion of the 10 min, racemic alcohol **15** (10.0 mg, 28.4 μmol, 1.00 equiv, in 100 μL of PhMe) was added to the reaction mixture. The suspension was then heated to 80 °C for 24 h. The reaction was allowed to cool to ambient temperature, and was then filtered through a small pad of Celite using toluene as eluent. The filtrate was concentrated in vacuo, and the residue was purified by flash chromatography using 10:90→15:85 EtOAc/hexanes to afford (3*R*,5*S*)-alcohol **15** as an oil (4.3 mg, 43% yield, 95% ee). $[\alpha]_D^{24.98}$ +26.4 (*c* 0.15, EtOAc).

4.7. Methyl-5-(5-acetoxy-3-hydroxycyclopent-1-en-1-yl)-3-methylfuran-2-carboxylate (16)

To a solution of alcohol **15** (96.0 mg, 0.270 mmol, 1.00 equiv) in pyridine (2.70 mL, 0.100 M) was added acetic anhydride (0.270 mL, 2.50 mmol, 9.00 equiv) and DMAP (3.30 mg, 0.0270, 0.100 equiv) at ambient temperature. The reaction was stirred until consumption of allylic alcohol **15** as monitored by TLC (ca. 30 min). The solution was cooled to 0 °C and diluted with EtOAc/brine (1:1). The layers were separated, and the aqueous solution was extracted 2× with EtOAc. The combined organic layer was successively washed with satd $CuSO_4$ (aq), H_2O, satd $NaHCO_3$ (aq), and brine. The organic layer was then dried with Na_2SO_4, filtered, and concentrated in vacuo to yield an allylic acetate that was taken directly on to the next reaction (101 mg, 95%). ^1H NMR (300 MHz, $CDCl_3$) δ 6.49 (dd, *J*=0.9, 2.1 Hz, 1H), 6.26 (s, 1H), 5.85 (dd, *J*=4.2, 7.5 Hz, 1H), 4.84 (m, 1H), 3.90 (s, 3H), 2.96 (dt, *J*=7.5, 14.4 Hz, 1H), 2.33 (s, 3H), 2.10 (s, 3H), 1.73 (m, 1H), 0.91 (s, 9H), 0.11 (s, 3H), 0.11 (s, 3H).

A solution of TBAF (0.290 mL of 1 M solution in THF, 0.289 mmol, 1.20 equiv) was added to the crude allylic acetate (95 mg, 0.241 mmol, 1.00 equiv) in THF (4.8 mL) at 0 °C. The reaction was allowed to warm to ambient temperature and monitored by TLC. Once complete, the reaction was diluted with H_2O, and the reaction was extracted 3× with EtOAc. The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The crude solid was purified by flash chromatography using 50:50, EtOAc/hexanes to provide allylic alcohol **16** as a white solid (64 mg, 85% from alcohol **15**): R_f 0.2 (40:60, EtOAc/hexanes, UV); ^1H NMR (500 MHz, $CDCl_3$) δ 6.60 (d, *J*=2.4 Hz, 1H), 6.29 (s, 1H), 5.88 (dd, *J*=2.9, 7.3 Hz, 1H), 4.83 (m, 1H), 3.88 (s, 3H), 2.88 (app. dt, *J*=14.7, 7.1, 1H), 2.32 (s, 3H), 2.07 (s, 3H), 1.81 (app. dt, *J*=12.2, 2.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 160.0, 150.6, 140.1, 134.6, 133.6, 132.6, 113.8, 75.7, 74.4, 51.7, 41.5, 21.3, 11.7; IR (film) 3424, 2953, 1712, 1598, 1511, 1440, 1374, 1297, 1240, 1197, 1104, 1035 cm^{-1}; HRMS (EI^+) calcd for $[C_{14}H_{16}O_6]^+$: *m*/*z* 280.2804, found 280.2800.

4.8. Methyl-5-(5-acetoxy-3-((2-diazo-3-oxobutanoyl)oxy)cyclopent-1-en-1-yl)-3-methylfuran-2-carboxylate (17)

To a solution of allylic alcohol **16** (15.0 mg, 0.0540 mmol, 1.00 equiv), 2-diazoacetoacetic acid (**14**, 16.7 mg, 0.130 mmol, 2.40 equiv), and DMAP (0.660 mg, 0.00540 mmol, 0.100 equiv) in CH_2Cl_2 (360 μL) at 23 °C, was added in one portion DCC (22.3 mg, 0.108 mmol, 2.00 equiv). The reaction was heated to 40 °C, monitored by TLC, and the reaction was complete in 60–90 min. The reaction was filtered through a pad of Celite (Et_2O eluent), and the resulting filtrate was partitioned between H_2O and Et_2O. The aqueous layer was extracted 2× with Et_2O. The organic extracts were combined, washed with $NaHCO_3$ (satd), and then with brine. The organic layer was dried over Na_2SO_4, concentrated in vacuo, and the resulting crude oil was purified by silica gel chromatography (80:20→75:25, hexanes/EtOAc) to yield ester **17** as a light-yellow solid (338 mg, 65% average). ^1H NMR (500 MHz, $CDCl_3$) δ 6.60 (d, *J*=2.2 Hz, 1H), 6.30 (s, 1H), 6.19 (m, 1H), 6.07 (m, 1H), 3.88 (s, 3H), 2.47 (s, 3H), 2.44 (m, 2H), 2.33 (s, 3H), 2.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.0, 170.8, 161.2, 159.8, 149.9, 140.5, 136.2, 132.5, 130.5, 114.7, 79.0, 76.2, 51.8, 39.1, 28.4, 21.2, 11.7; IR (film) 2142, 1713, 1657, 1295, 1237 cm^{-1}; HRMS (EI^+) calcd for $[C_{18}H_{18}N_2O_8]^+$: *m*/*z* 390.1063, found 390.1061.

4.9. Methyl-5-(3-acetoxy-2a-acetyl-2-oxohexahydro-2*H*-1-oxacyclopropa[*cd*]pentalen-2b-yl)-3-methylfuran-2-carboxylate (18)

4.9.1. Microwave conditions. The microwave was pre-warmed by undergoing an actual run with just DCE in the reaction tube. A solution of compound **17** (45.0 mg, 0.120 mmol, 1.00 equiv) and $Cu(TBSal)_2$ (5.00 mg, 0.0120 mmol, 0.100 equiv) in DCE (3.00 mL) was heated for 20 min at 105 °C in the microwave. The following parameters for the microwave are as follows: Power=150 W, Temperature=105 °C, Pressure=200 atm, Ramp=1 min, Run time=20 min. The reaction was concentrated in vacuo, and the resulting crude oil was purified by silica gel chromatography (40:60 EtOAc/hexanes) to yield cyclopropane **18** as a white solid (21 mg, 55%). ^1H NMR (500 MHz, C_6D_6) δ 6.20 (s, 1H), 5.47 (dd, *J*=1.7, 7.3 Hz, 1H), 4.01 (m, 1H), 3.53 (d, *J*=4.6 Hz, 1H), 3.39 (s, 3H), 2.39 (s, 3H), 2.13 (s, 3H), 1.73 (d, *J*=14.4 Hz, 1H), 1.71 (s, 3H), 1.29 (ddd, *J*=3.4, 7.6, 14.6 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 195.7, 170.8, 170.5, 160.0, 150.8, 141.5, 132.8, 116.2, 81.6, 78.4, 52.8, 51.9, 50.4, 46.0, 45.8, 29.7,

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20.8, 12.0; IR (film) 2954, 1770, 1747, 1714, 1230 cm^{-1}; HRMS (EI^+) calcd for $[C_{18}H_{19}O_8]^+$: *m*/*z* 363.1080, found 363.1085.

4.9.2. Thermal conditions. A solution of $Cu(TBSal)_2$ (1.30 mg, 0.00300 mmol, 0.0200 equiv) in toluene (2.40 mL) was heated under Ar to 108 °C. A warm solution of diazo **17** (62.0 mg, 0.150 mmol, 1.00 equiv) in toluene (0.400 mL) was added dropwise over 6 min. The reaction was heated to 112 °C, and monitored by TLC (40:60 EtOAc/hexanes). After 100 min, the reaction was complete, and allowed to cool to ambient temperature. The solvent was removed in vacuo, and the dark residue was purified by flash chromatography (40:60 EtOAc/hexanes) to provide cyclopropane **18** (35 mg, 56%).

4.10. Methyl-5-(2a-acetyl-3-hydroxy-2-oxohexahydro-2*H*-1-oxacyclopropa[*cd*]pentalen-2a1-yl)-3-methylfuran-2-carboxylate (20)

K_2CO_3 (32.0 mg, 0.240 mmol, 2.00 equiv) was added to a solution of cyclopropane **18** (43.0 mg, 0.120 mmol, 1.00 equiv) in MeOH (2.30 mL) at 0 °C. The reaction was stirred at 0 °C and monitored by TLC. Once complete, the reaction was diluted with satd NH_4Cl (aq) and EtOAc, the layers were then separated, and the aqueous layer was further extracted 2× with EtOAc. The organic layers were combined, washed with H_2O and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to afford a crude oil. The latter oil was purified by silica gel chromatography (50:50 EtOAc/hexanes) to provide alcohol **20** as a glue (30 mg, 80%). ^1H NMR (500 MHz, C_6D_6) δ 5.66 (s, 1H), 4.69 (m, 1H), 4.03 (app. q, *J*=1.7, 5.6 Hz, 1H), 3.42 (s, 3H), 3.34 (d, *J*=5.6 Hz, 1H), 2.28 (s, 3H), 2.12 (s, 3H), 1.53 (d, *J*=14.4 Hz, 1H), 1.13 (ddd, *J*=3.4, 7.3, 14.4 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 209.4, 196.2, 171.1, 159.6, 148.7, 141.6, 132.3, 114.6, 84.0, 71.5, 58.4, 51.4, 46.8, 45.9, 29.8, 11.8; IR (film) 3469, 1770, 1706, 1299, 1081 cm^{-1}; HRMS (EI^+) calcd for $[C_{16}H_{16}O_7Na]^+$: *m*/*z* 343.0794, found 343.0811.

4.11. Methyl-5-(2a-acetyl-2,3-dioxohexahydro-2*H*-1-oxacyclopropa[*cd*]pentalen-2a^1-yl)-3-methylfuran-2-carboxylate (21)

To a solution of alcohol **20** (62.0 mg, 0.190 mmol, 1.00 equiv) in CH_2Cl_2 (3.90 mL) was added Dess–Martin periodinane (160 mg, 0.390 mmol, 2.00 equiv), and the resulting slurry was stirred until consumption of starting material (ca. 1 h). The reaction was diluted with EtOAc and a 1:1 ratio of satd $Na_2S_2O_4$ (aq): satd $NaHCO_3$ (aq), and stirred vigorously for 5 min. The layers were separated and the organic layer was washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo to yield crude ketone **21** as a colorless oil (60 mg, 97%). Ketone **21** was carried on crude as attempts toward further purification resulted in decomposition. ^1H NMR (500 MHz, C_6D_6) δ 5.53 (s, 1H), 4.59 (dd, *J*=1.2, 4.4 Hz, 1H), 3.49 (d, *J*=1.2 Hz, 1H), 3.43 (s, 3H), 2.07 (s, 3H), 2.00 (s, 3H), 1.90 (d, *J*=17.6 Hz, 1H), 1.66 (dd, *J*=4.6, 17.6 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 202.0, 193.2, 168.7, 159.6, 146.2, 140.0, 142.4, 132.3, 115.9, 78.4, 54.4, 52.6, 51.6, 49.9, 45.3, 29.5, 11.8; IR (film) 2924, 2854, 1180, 1750, 1715, 1559, 1438, 1294, 1102 cm^{-1}; HRMS (EI^+) calcd for $[C_{16}H_{14}O_7]^+$: *m*/*z* 318.0740, found 318.0732.

4.12. Methyl-5-(3-acetyl-5-hydroxy-4,6a-dimethoxy-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-4-yl)-3-methylfuran-2-carboxylate (22)

Crude ketone **21** (11.0 mg, 0.0340 mmol, 1.00 equiv) and $La(OTf)_3$ (20.0 mg, 0.0340 mmol, 1.00 equiv) were dissolved in MeOH (0.670 mL) at ambient temperature, then heated to 55 °C and the reaction was stirred until the majority of starting material appeared consumed by TLC. The reaction was diluted with EtOAc and H_2O and the aqueous layer was extracted 3× with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using 66:34 EtOAc/hexanes to afford alcohol **22** as an oil (8.0 mg, 55%); ^1H NMR (500 MHz, C_6D_6) δ 5.90 (s, 1H), 4.26 (dd, *J*=1.7, 5.6 Hz, 1H), 4.24 (m, 1H), 4.04 (d, *J*=5.8 Hz, 1H), 3.38 (s, 3H), 3.20 (s, 3H), 2.80 (s, 3H), 2.56 (dd, *J*=4.2, 14.2 Hz, 1H), 2.26 (s, 3H), 2.20 (d, *J*=14.2 Hz, 1H), 2.15 (s, 3H), 1.84 (d, *J*=2.7 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 199.3, 170.6, 159.8, 154.1, 140.9, 132.0, 119.4, 115.9, 87.4, 76.9, 60.5, 52.0, 51.5, 51.4, 48.0, 43.7, 29.5, 11.8; IR (film) 3465, 2955, 1771, 1722, 1441, 1297, 1197, 1102 cm^{-1}; HRMS (EI^+) calcd for $[C_{18}H_{22}O_9]^+$: *m*/*z* 382.1264, found 382.1259.

4.13. Methyl-5-((*E*)-5-((4-bromobenzoyl)oxy)-3-(1-((4-bromobenzoyl)oxy)ethylidene)-4,6a-dimethoxy-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-4-yl)-3-methylfuran-2-carboxylate (23)

Triethylamine (19.0 μL, 0.140 mmol, 2.40 equiv) was added at ambient temperature to a solution of alcohol **22** (22.0 mg, 0.0580 mmol, 1.00 equiv) in CH_2Cl_2 (310 μL). DMAP (0.700 mg, 0.00580 mmol, 0.100 equiv) and *p*-bromobenzoyl bromide (28.0 mg, 0.130 mmol, 2.20 equiv) were then added, and the reaction was stirred for 1 h at ambient temperature. The reaction was diluted with EtOAc and H_2O, the layers were separated, and the aqueous layer was extracted once with EtOAc. The EtOAc layers were combined, washed with satd $NaHCO_3$ (aq), washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. Crystals suitable for X-ray analysis were obtained by crystallization of crude furan **23** (30 mg, yield 70%) from EtOAc/heptane. ^1H NMR (500 MHz, C_6D_6) δ 7.97 (m, 2H), 7.39 (m, 2H), 7.25 (m, 2H), 7.10 (m, 2H), 5.99 (s, 1H), 5.73 (m, 1H), 3.93 (s, 1H), 3.24 (s, 3H), 3.13 (s, 3H), 2.88 (s, 3H), 2.54 (s, 3H), 2.49 (m, 2H), 2.15 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 168.1, 164.6, 161.9, 161.6, 159.2, 152.9, 141.0, 132.1, 132.0, 132.0, 131.8, 131.4, 129.3, 128.8, 128.6, 127.7, 114.9, 114.7, 114.2, 87.4, 78.1, 55.5, 52.3, 51.6, 50.1, 39.3, 17.4, 11.4; IR (film) 2948, 1762, 1725, 1589, 1227, 1101, 1070, 1010 cm^{-1}; HRMS (FAB^+) calcd for $[C_{32}H_{30}O_{11}Br^{81}Br]^+$: *m*/*z* 750.0135, found 750.0159. Mp=175–177 °C (heptane/EtOAc).

4.14. Methyl-5-(2a-acetyl-3-((benzyloxy)methoxy)-2-oxohexahydro-2*H*-1-oxacyclopropa[*cd*]pentalen-2b-yl)-3-methylfuran-2-carboxylate (24)

Cyclopropane **24** was obtained from allylic alcohol **15** using the same generic route employed to obtain cyclopropane **18**. For the cyclopropanation reaction, cyclopropane **24** was obtained as an oil (3.5 mg, 74%). ^1H NMR (500 MHz, C_6D_6) δ 7.30 (d, *J*=8.3 Hz, 2H), 7.13 (d, *J*=7.6 Hz, 1H), 7.06 (t, *J*=7.3 Hz, 2H), 5.93 (s, 1H), 4.93 (d, *J*=7.1 Hz, 1H), 4.63 (d, *J*=7.1 Hz, 1H), 4.60 (s, 2H), 4.11 (m, 1H), 3.42 (d, *J*=4.6 Hz, 1H), 3.39 (s, 3H), 2.42 (s, 3H), 2.12 (s, 3H), 1.86 (d, *J*=14.2 Hz, 1H), 1.20 (dd, *J*=3.2, 14.2 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 195.0, 169.4, 158.9, 150.4, 140.4, 138.0, 131.4, 128.2, 114.2, 93.3, 80.7, 69.7, 51.4, 50.6, 50.3, 44.8, 28.6, 11.1; IR (film) 2952, 1769, 1713, 1297, 1102, 1037 cm^{-1}; HRMS (EI^+) calcd for $[C_{24}H_{23}DO_8]^+$: *m*/*z* 441.1534, found 441.1523.

4.15. Methyl-5-(2a-acetyl-3-(methoxymethoxy)-2-oxohexahydro-2*H*-1-oxacyclopropa[*cd*]pentalen-2b-yl)-3-methylfuran-2-carboxylate (25)

Cyclopropane **25** was obtained from allylic alcohol **15** using the same generic route employed to obtain cyclopropane **18**. For the cyclopropanation reaction, cyclopropane **25** was obtained as an oil

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(2.3 mg, 62%). ^{1}H NMR (500 MHz, C_6D_6) δ 5.95 (s, 1H), 4.78 (d, J=7.1 Hz, 1H), 4.48 (d, J=7.1 Hz), 4.09 (m, 1H), 3.43 (d, J=4.9, 1H), 3.39 (s, 3H), 3.23 (s, 3H), 2.43 (s, 3H), 2.13 (s, 3H), 1.82 (d, J=14.2, 1H), 1.20 (dd, J=3.4, 14.2 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 196.0, 170.3, 159.8, 151.3, 141.2, 132.3, 115.0, 96.1, 81.5, 56.3, 52.3, 51.5, 51.1, 45.8, 45.7, 29.4, 12.0; IR (film) 2926, 1767, 1711, 1402, 1297, 1100 cm^{-1}; HRMS (EI$^+$) calcd for $[C_{18}H_{19}DO_8]^+$: m/z 365.1221, found 365.1216.

4.16. Methyl-5-(2a-acetyl-2-oxo-3-((2-(trimethylsilyl)ethoxy) methoxy)hexahydro-2*H*-1-oxacyclopropa[*cd*]pentalen-2b-yl)-3-methylfuran-2-carboxylate (26)

Cyclopropane **26** was obtained from allylic alcohol **15** using the same generic route employed to obtain cyclopropane **18**. For the cyclopropanation reaction, cyclopropane **26** was obtained as an oil (2.9 mg, 62%). ^{1}H NMR (500 MHz, C_6D_6) δ 6.02 (s, 1H), 4.94 (d, J=7.1 Hz, 1H), 4.65 (d, J=7.1 Hz, 1H), 4.13–4.11 (m, 1H), 3.78–3.73 (m, 1H), 3.46 (d, J=4.6 Hz, 1H), 3.42 (s, 3H), 2.44 (s, 3H), 2.15 (s, 3H), 1.93 (d, J=14.2 Hz, 1H), 1.27 (dd, J=3.2, 13.9 Hz, 1H), 0.94–0.90 (m), 0.01 (s, 9H); ^{13}C NMR (125 MHz, C_6D_6) δ 196.0, 170.3, 159.8, 151.5, 141.2, 132.4, 115.2, 94.3, 81.6, 66.5, 56.2, 51.6, 51.1, 45.9, 46.0, 29.5, 18.6, 12.0, −0.80; IR (film) 2953, 1770, 1713, 1440, 1297 cm^{-1}; HRMS (FAB$^+$) calcd for $[C_{22}H_{29}DO_8SiNa]^+$: m/z 474.1773, found 474.1675.

4.17. Methyl-5-(2a-acetyl-3-((*tert*-butyldimethylsilyl)oxy)-2-oxohexahydro-2*H*-1-oxacyclopropa[*cd*]pentalen-2b-yl)-3-methylfuran-2-carboxylate (27)

Cyclopropane **27** was obtained from allylic alcohol **15** using the same generic route employed to obtain cyclopropane **18**. For the cyclopropanation reaction, cyclopropane **27** was obtained as an oil (6.5 mg, 71%). ^{1}H NMR (500 MHz, C_6D_6) δ 5.71 (s, 1H), 4.15–4.13 (m, 1H), 3.42 (s, 3H), 3.33 (d, J=4.6 Hz, 1H), 2.45 (s, 3H), 2.13 (s, 3H), 1.63 (d, J=13.7 Hz, 1H), 1.21 (dd, J=3.4, 13.7 Hz, 1H), 1.09 (s, 9H), 0.29 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 196.3, 170.2, 159.7, 151.2, 141.4, 132.0, 114.4, 81.6, 53.6, 52.6, 51.4, 48.2, 45.3, 29.4, 26.3, 18.8, 11.9, −4.5, −4.6; IR (film) 2953, 2930, 2857, 1770, 1714, 1297, 1113 cm^{-1}; HRMS (FAB$^+$) calcd for $[C_{22}H_{29}DO_7SiNa]^+$: m/z 459.1800, found 458.1749.

4.18. Methyl-5-(2a-acetyl-3-((2-methoxyethoxy)methoxy)-2-oxohexahydro-2*H*-1-oxacyclopropa[*cd*]pentalen-2b-yl)-3-methylfuran-2-carboxylate (28)

Cyclopropane **28** was obtained from allylic alcohol **15** using the same generic route employed to obtain cyclopropane **18**. For the cyclopropanation reaction, thermal conditions were used, and cyclopropane **28** was obtained as an oil (9.1 mg, 42%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.23 (s, 1H), 5.11 (m, 1H), 5.02 (d, J=7.1 Hz, 1H), 4.92 (d, J=7.1 Hz, 1H), 3.99 (d, J=4.9 Hz, 1H), 3.86 (s, 3H), 3.83 (q, J=4.4 Hz, 2H), 3.58 (t, J=4.4 Hz, 2H), 3.39 (s, 3H), 2.46 (s, 3H), 2.34 (d, J=14.2 Hz, 1H), 2.29 (s, 3H), 2.20 (dd, J=3.2, 14.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.2, 170.1, 159.4, 149.8, 140.2, 131.9, 114.7, 94.3, 81.5, 71.6, 67.4, 59.0, 51.6, 51.4, 50.9, 45.4, 45.2, 29.1, 11.6; IR (film) 2925, 1767, 1711, 1613, 1548, 1440, 1297, 1198, 1099, 1037 cm^{-1}; HRMS (EI$^+$) calcd for $[C_{20}H_{23}DNaO_9]^+$: m/z 432.1381, found 432.1365.

4.19. Methyl-5-(3-acetyl-5-hydroxy-4-methoxy-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-4-yl)-3-methylfuran-2-carboxylate (32)

Furan **20** (49.0 mg, 0.153 mmol, 1.00 equiv) and La(OTf)$_3$ (89.5 mg, 0.153 μmol, 1.00 equiv) were dissolved in MeOH (3.00 mL) at ambient temperature, and then heated to 55 °C and the reaction was stirred for 1–2 h. The reaction was diluted with EtOAc and H_2O and the aqueous layer was extracted 3× with EtOAc. The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography using 60:40 EtOAc/hexanes to afford alcohol **32** as an oil (35 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.34 (s, 1H), 5.30 (br, 1H), 5.17 (t, J=7.3 Hz, 1H), 4.64 (d, J=3.8 Hz, 1H), 4.10 (t, J=6.7 Hz, 1H), 3.91 (d, J=5.5 Hz, 1H), 3.89 (s, 3H), 3.03 (s, 3H) 2.50 (ddd, J=4.1, 7.1, 15.4 Hz, 1H), 2.43 (s, 3H), 2.47 (s, 3H), 2.20 (d, J=15.4 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_6) δ 200.0, 172.4, 159.9, 154.3, 140.9, 132.1, 116.2, 88.5, 83.5, 77.0, 58.6, 51.4, 51.4, 45.9, 40.0, 29.6, 11.8; IR (film) 3474, 2952, 1769, 1717, 1297, 1195, 1098 cm^{-1}; HRMS (EI$^+$) calcd for $[C_{17}H_{21}O_8Na]^+$: m/z 353.1236, found 353.1246.

4.20. Methyl-5-((*E*)-3-(1-((4-bromobenzoyl)oxy)ethylidene)-5-hydroxy-4-methoxy-2-oxohexahydro-2*H*-cyclopenta[*b*]furan-4-yl)-3-methylfuran-2-carboxylate (33)

Triethylamine (43.0 μL, 306 μmol, 4.00 equiv) was added at 0 °C and under N_2, to a solution of alcohol **32** (27.0 mg, 76.6 μmol, 1.00 equiv) in CH_2Cl_2 (955 μL). After 1 min, *p*-bromobenzoyl bromide (42.0 mg, 192 μmol, 2.50 equiv) was added, and the reaction was stirred for 30 min at 0 °C. The reaction was allowed to warm to ambient temperature and stir for an additional 1 h. The reaction was then diluted with Et_2O and H_2O, the layers were separated, and the aqueous layer was extracted once with Et_2O. The Et_2O layers were combined, washed with satd $NaHCO_3$ (aq), washed with brine, dried with $MgSO_4$, filtered, and concentrated in vacuo. Crystals suitable for X-ray analysis were obtained by crystallization of crude furan **33** (54 mg, 98% yield) from EtOAc/heptane. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J=8.5 Hz, 2H), 7.62 (d, J=8.5 Hz, 2H), 6.38 (s, 1H) 5.06 (t, J=6.4 Hz, 1H), 4.46 (q, J=7.2, 3.5 Hz, 1H), 3.80 (m, 4H), 3.18 (s, 3H), 2.45 (s, 3H), 2.37 (m, 1H), 2.33 (s, 3H), 2.28 (d, J=3.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.5, 162.0, 159.9, 153.5, 139.9, 132.0, 131.9, 131.6, 129.2, 129.0, 127.6, 115.8, 115.3, 88.7, 79.8, 52.6, 52.3, 51.5, 38.5, 17.1, 11.6; IR (film) 3445, 2950, 1749, 1705, 1589, 1439, 1399, 1300, 1231, 1070, 1010 cm^{-1}; HRMS (EI$^+$) calcd for $[C_{24}H_{23}BrO_9]^+$: m/z 557.0423, found 557.0427. Mp=158–159 °C (EtOAc/heptane).

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18. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 602164 for compound **23**.
19. All compounds in Fig. 2 had partial deuterium incorporation at C(5).
20. In this system, the donor moiety is the furan ring, and the acceptor species is the β-ketoester.
21. Spartan calculations (semi-empirical, AM1) show that undesired alcohol **20** is 4.3 kcal lower in energy than desired alcohol **19**.
22. Crystallographic data have been deposited at the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK and copies can be obtained on request, free of charge, by quoting the publication citation and the deposition number 606989 for compound **33**.

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