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A C–H oxidation approach for streamlining synthesis of chiral polyoxygenated motifs

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^cDedicated to Professor Paul Wender for his pioneering and inspirational work on complexity generating organometallic reactions for streamlining complex molecule synthesis.

Abstract

Chiral oxygenated molecules are pervasive in natural products and medicinal agents; however, their chemical syntheses often necessitate numerous, wasteful steps involving functional group and oxidation state manipulations. Herein a strategy for synthesizing a readily diversifiable class of chiral building blocks, allylic alcohols, through sequential asymmetric C–H activation/resolution is evaluated against the state-of-the-art. The C–H oxidation routes' capacity to strategically introduce oxygen into a sequence and thereby minimize non-productive manipulations is demonstrated to effect significant decreases in overall step-count and increases in yield and synthetic flexibility.

Keywords

C–H oxidation; Allylic oxidation; Allylic alcohols; Enantioselective; Palladium; Sulfoxide

1. Introduction

Polyoxygenation in natural products and medicinal agents is ubiquitous and often confers specific biological function to small molecules. Most traditional organic sequences for assembling such motifs involve acid/base reactions to install the oxygenated functionality as the hydrocarbon core is being constructed. Though reliable, these routes require significant synthetic overhead, commonly in the form of protection/deprotection sequences, oxidation state changes, and functional group manipulations (FGMs). Our group and others have

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Supplementary Material Full experimental details for all compounds synthesized and copies of ¹H and ¹³C NMR spectra as well as chiral GC and HPLC traces for chiral compounds as well as crystallographic data on *p*-Bromophenyl (–)-**20** are available. Supplementary data related to this article can be found at <http://>

demonstrated that selective hydrocarbon C—H oxidation presents an alternative approach by directly installing oxidation when it is most synthetically appropriate and by significantly reducing the number of reactive functional groups that must be carried through and consequently manipulated in a sequence.^{1,2,3} Herein, we utilize an asymmetric branched allylic C—H oxidation in combination with enzymatic and small molecule resolution methods to interrogate the streamlining effect of such processes for the construction of chiral polyoxygenated motifs.⁴

Allylic alcohols such as those shown in Scheme 1 are prevalent, in part due to ease with which they can be further elaborated. Such motifs are particularly challenging to construct asymmetrically when the oxygen atom is remote from other functionality, rendering stereochemical relay approaches unviable.^{5,6} Most often, these products are obtained through a kinetic resolution of the racemic alcohol obtained by the addition of a vinyl carbanion to an aldehyde.^{5h-i} Additionally, Sharpless asymmetric epoxidation (SAE) of linear allylic alcohols followed by two-step sequences to install the vinyl moiety can be employed.^{5f-g,7} In general, both of these strategies begin with preoxidized starting materials that are elaborated toward the target through carbanion based reactions that, due to low chemoselectivities, demand lengthy sequences of FGMs.

Palladium (II)/sulfoxide catalysis has proven itself to be a general platform for allylic C—H esterification,^{8a-d} amination,^{9b,c,e-g,j} alkylation,^{10a-c} and dehydrogenation¹¹ of terminal olefins under mildly acidic, oxidative conditions. We previously reported a Pd(II)-bis-sulfoxide **1**/chiral Cr(salen)F **2** catalyzed reaction for the asymmetric branched allylic C—H oxidation (ABAO) of terminal olefins (Scheme 1).⁴ This reaction proceeds under mild conditions with high functional group tolerance and chemoselectivity (primary alcohols and internal olefins are well tolerated) to furnish enantioenriched allylic alcohols in good yields. Although enantioselectivities are modest (43-63% ee) these represent the best to date for C—H activation of this challenging olefin class.¹² We hypothesized that combining the asymmetric branched allylic oxidation (ABAO) with enzymatic and/or small-molecule-catalyst based resolutions would enable us to develop streamlined routes to chiral allylic alcohols by circumventing the FGMs of traditional carbanion based approaches. In addition, even the modest enantioenrichment afforded by the ABAO would lead to significant improvements in yield for subsequent resolution steps as compared to racemic approaches (e.g. at 60% ee, 80:20 e.r., only 20% of the material is lost in a highly efficient resolution).

2. Results

We began our explorations by targeting a prototypical *bis*-oxygenated chiral building block (–)-**3**, a precursor to the C19 – C26 fragment of the potential cancer therapeutic Bistramide A (Scheme 2).^{13a} In the traditional carbanion based route, diol **4** is selectively protected at one terminus and then oxidized and subjected to a Horner-Wadsworth-Emmons olefination at the other end to generate ester **5**.^{13c-d} After reduction of the ester, SAE affords the epoxy alcohol in 93% ee.^{13e-f} The primary alcohol is then converted to a halogen, which is eliminated with zinc to afford the desired allylic alcohol (–)-**3** in a total of 7 steps and 34% overall yield.^{13a,14}

Alternatively, using an oxidation driven route, after simple protection of commercially available **7**, allylic C—H oxidation installs the oxygen functionality directly at the desired oxidation state, with significant enrichment toward the desired enantiomer (45% ee, 72:28 e.r.). Subsequent methanolysis and enzymatic resolution via acylation of the minor enantiomer by commercially available Novozyme 435™ gives enantiopure (–)-**3** in a total of 4 steps and 47% overall yield. The C–H oxidation route significantly reduces the overall step count and improves the overall yield by reducing FGMs and oxidation state changes (Scheme 2). Additionally, we found that the C–H oxidation sequence requires only two purifications, further enabling rapid access to these chiral building blocks.¹⁵

Broad use of an enantioselective transformation requires that either enantiomer of the desired product can be produced with high enantioselectivity. Chiral Cr(salen)F **2** is readily available as either the (*R,R*)- or (*S,S*)-enantiomer, and careful selection of commercially available enzymes allows for enrichment of either stereoisomer of the product.¹⁶ To demonstrate this, we used Pd(II)/bis-sulfoxide **1**/*(S,S)*-**2** and resolution with the commercially available protease *Subtilisin Carlsberg* to generate (+)-**3** in 99%ee and nearly identical overall yield to the route previously described for (–)-**3** (Scheme 2, 3). This matches the flexibility of other catalyst-controlled approaches to these compounds, like the SAE which was utilized to make (+)-**3** in a total synthesis of the potent biotoxin Azaspiracid A.^{13,14}

We next sought to compare the asymmetric C–H oxidation route to chiral allylic alcohols to traditional resolution strategies. Ester (–)-**9** was synthesized *en route* to the potent flower inducing factor 9R-KODA (Scheme 4).¹⁷ In order to avoid a lengthy sequence of FGMs, the carbanion based route started with ozonolysis of methyl oleate (**10**) followed by direct vinylation of the resultant aldehyde in the presence of an ester group. While the poor chemoselectivity of this approach resulted in a significant diminishment in overall yield, rapid access to (±)-**9** was achieved. Subsequent enzymatic kinetic resolution afforded enantiopure (–)-**9** in only three steps, however, with an overall yield of only 9%. Conversely, ABAO of commercially available α-olefin **12** followed by methanolysis and enzymatic resolution yielded (–)-**9** with an equivalent step count and enantiopurity, *but with a 5-fold increase in total yield* (3 steps, 53% yield, 99%ee). High chemoselectivity and functional group tolerance is a general feature of all of the Pd(II)/bis-sulfoxide catalyzed allylic C–H oxidations reported to date and renders them well-suited towards introduction of oxidized functionality late in synthetic sequences.^{3c-g} Importantly, this reaction sequence was run on gram scale with virtually no diminishment in yield (49% versus 53% overall yield).

Due to the large number of commercially available α-olefin starting materials, the C–H oxidation sequences presented so far have begun with fully constructed carbon frameworks. We next sought to evaluate cases in which the α-olefin is not available to determine if a C–H oxidation route was still competitive with traditional approaches. Synthesis of allylic alcohol (–)-**13** towards (+)-iso-6-cassine began from a commercially available, protected bromide **14** (Scheme 5).¹⁸ Formation of a Grignard reagent from bromide **14** followed by its addition into acrolein gave racemic alcohol (±)-**13** in one step.^{18b} Again, this carbanion-based carbonyl alkylation reaction proceeds with poor chemoselectivity, giving a mixture of

1,2 and 1,4 acrolein addition products. Enzymatic resolution yielded the desired (–)-**13** in two steps and 19% overall yield.^{18a} From the same commercially available bromide **14**, a suitable starting material for C–H oxidation can be obtained directly by allylation, a C–C bond forming reaction without the chemoselectivity issues that limited the traditional route. Subjecting the resultant olefin to the allylic C–H oxidation/methanolysis/enzymatic resolution sequence affords the desired enantiopure alcohol (–)-**13** in four steps and 46% overall yield, more than doubling the yield of the traditional route. This is enabled by the ease of installing inert α -olefin moieties through powerful allylation methods and the selective nature of these C–H oxidation reactions.

We have demonstrated how the ABAO can be combined with enzymatic resolution to afford enantiopure allylic alcohols rapidly and in good yield. However, powerful, small-molecule catalyst-controlled enantioselective transformations can also be used to enrich the products of this C–H oxidation. We sought to explore this approach to chiral polyol synthesis through construction of the densely functionalized furan core of Goniothalesdiol. Due to its potent activity against mouse leukemia cells, a number of total syntheses of Goniothalesdiol (**15**) and its epimers have been undertaken.^{19b-1} Generally these routes begin with chiral pool materials; however they lack the synthetic flexibility to rapidly access derivatives of **15**. One approach initially developed by Gracza and co-workers to **15** proceeds through the tetrasubstituted furan core **16**.^{19b} We recognized that an unprecedented Pd(II)/bis-sulfoxide-catalyzed tandem ABAO/oxidative Heck sequence could access this core structure rapidly (Scheme 6).²⁰ Subsequent Sharpless asymmetric dihydroxylation (SAD) would generate separable diastereomers, allowing us to obtain enantiopure material for further reaction.²¹ Significantly, our *de novo* approach to **16** is quite flexible, allowing us to selectively control the stereochemistry at the 5, 6, and 7 positions of the core furan as well as easily vary the nature of the aryl substituent at position 7. While previous syntheses have relied primarily on C–C bond forming reactions, this plan involves a steady increase in complexity through hydrocarbon oxidations.

We decided upon furan core (–)-**22** as an interesting target for this strategy because, to the best of our knowledge, 6-*epi*-Goniothalesdiol has yet be synthesized or evaluated medicinally. Our route began with the Pd(II)/bis-sulfoxide-catalyzed tandem ABAO/oxidative Heck sequence. Asymmetric branched allylic C–H oxidation (ABAO) reaction on methyl ester **17**, followed by the addition of phenyl boronic acid directly furnished ester **18** that was taken on crude through hydrolysis and cyclization to give lactone **19** in 54% yield (two steps) and 50% *ee* (75:25 e.r.).

Sharpless asymmetric dihydroxylation (SAD) of **19** and subsequent ketal protection of the resultant diol, gave 70% of diastereomerically and enantiomerically pure (–)-**20**.²² Selenation /dehydroselenation of lactone (–)-**20** afforded unsaturated γ -lactone (+)-**21** in 73% yield. Deprotection of the acetonide followed by *in situ* DIPEA assisted cyclization afforded the desired tetrasubstituted pyran (–)-**22** in 7 total steps and 22% overall yield. Previous C–C bond forming routes to this core structure proceeded in 8 and 10 steps with 6% and 9% overall yields respectively. This case study demonstrates the streamlining potential of hydrocarbon oxidations for synthesizing densely functionalized fragments.

3. Conclusions

In summary, we have established that the asymmetric branched allylic oxidation reaction⁴ can be combined with other enantioselective transformations to afford enantiopure, polyoxygenated allylic alcohols rapidly and in good yields. This C–H oxidation approach is demonstrated to be advantageous to commonly used resolution and *de novo* synthetic strategies that require significant numbers of protection/deprotection steps and functional group manipulations. Strategies such as these, fueled by novel reactions, have the greatest potential to both transform synthetic planning and streamline chemical synthesis.²⁴

Experimental section

4.1 General information

All commercially obtained reagents were used as received; Achiral gas chromatographic (GC) analyses were performed on Agilent Technologies 6890N Series instrument equipped with FID detectors using a HP-5 (5%-Phenyl)-methylpolysiloxane column (30m, 0.32mm, 0.25 μ m). Chiral gas chromatographic (GC) analyses were performed on an Agilent Technologies 5890A Series instrument equipped with an FID detector using a J&W Scientific β -cyclodextrin column (30m, 0.25mm, 0.25 μ m). Thin-layer chromatography (TLC) was conducted with E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized with UV, potassium permanganate, and ceric ammonium molybdate staining. Flash column chromatography was performed as described by Still et al. using EM reagent silica gel 60 (230–400 mesh).²³ ¹H NMR spectra are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm). Data reported as: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration. Proton-decoupled ¹³C- NMR spectra were reported in ppm using solvent as an internal standard (CDCl₃ at 77.0 ppm). IR spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum BX and are reported in frequency of absorption (cm⁻¹). High-resolution mass spectra were obtained at the University of Illinois Mass Spectrometry Laboratory.

4.2 Experimental section

4.2.1 General procedure for asymmetric branched allylic acetoxylation—A vial (8 mL borosilicate) was charged with the following: 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (**1**) (10 mol%, 0.10 mmol, 50 mg); (1*R*,2*R*)-(–)-[1,2-Cyclohexanediamino-*N,N'*-bis(3,5-di-*t*-butylsalicylidene)] Chromium(III)F (R,R-**2**) (10 mol %, 0.10 mmol, 61.6 mg), 1,4-benzoquinone (2 equiv., 2.0 mmol, 216 mg), an activated 4Å MS bead (~30 mg), and a Teflon© stir bar. A separate vial (2 mL, borosilicate) was charged with the following: substrate (1.0 mmol), AcOH (1.1 equiv., 63 μ L), and EtOAc (200 μ L). The liquids were transferred to the solids via pipette and the vial rinsed with EtOAc (3 \times 100 μ L). After carefully stirring for 48 hrs at room temperature, the reaction mixture was transferred to a separatory funnel with ~3 mL EtOAc and diluted with hexanes (200 mL). The organic layer was rinsed with sat. aq. NaHSO₃ (1 \times 50 mL) and 5% aq. K₂CO₃ (2 \times 50 mL). Caution should be taken when combining aqueous layers as carbon dioxide is evolved. The combined aqueous layers were back extracted with hexanes (100 mL). The combined organic layers were dried (MgSO₄), filtered, and reduced *in vacuo*. The resulting oil was re-

dissolved in hexanes (50 mL) and extracted again with 5% aq. K_2CO_3 (3×10 mL) to remove residual hydroquinone. The organic layer was again dried ($MgSO_4$), filtered and reduced *in vacuo* to afford a clean mixture of allylic oxidation products and any unreacted starting material from which the B:L, yield, and conversions were determined (1H NMR). Unless otherwise noted, this material was taken forward without further purification, though each substrate was isolated at least once for characterization purposes. Reported yields and selectivities are an average of at least two runs. Enantiomeric excess was determined by chiral GC (β -cyclodextrin column), as compared to racemic standards generated through our standard branched oxidation chemistry.^{8a,b} Slight variations in B:L ratios and ee's were noted based on batch of Cr catalyst.

4.2.2 General procedure for cleavage of allylic acetates—To a 25 mL flask containing crude allylic acetate (1 mmol, assumed) was added MeOH (5 mL, 0.2 M) and potassium carbonate (0.276 g, 2 mmol). The reaction was vigorously stirred and monitored via thin layer chromatography (TLC). Upon completion, the reaction was transferred to a separatory funnel with methylene chloride (50 mL). Water (15 mL) was added, and the aqueous layer was extracted with methylene chloride (3×50 mL). The combined organics were washed with brine (1×10 mL), then dried ($MgSO_4$), filtered, and reduced *in vacuo*. Products were then purified by standard SiO_2 chromatography. While the branched and linear allylic alcohols were commonly separable, it was found that carrying them forward as a mixture had no detrimental effect as the subsequent resolution acylated the linear alcohol rapidly making its separation from branched alcohol trivial. Individual product yields and characterization are reported below.

4.2.2.1 (4R)-1-O-Benzyl-4-acetoxy-5-hexen-1,4-diol 3-OAc: Following the general procedure for the asymmetric branched allylic oxidation afforded: Run 1: 226 mg, 0.910 mmol, 91% yield; [B:L] = 4.7:1, [ee] = 44%. Run 2: 220 mg, 0.886 mmol, 89% yield; [B:L] = 3.8:1, [ee] = 45%. (β -cyclodextrin, 120°C isothermal, $t_R(R)$ = 64.98 min., $t_R(S)$ = 66.64 min.), [average yield: 90%.]; This material was taken forward without further purification. 1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 5.77 (ddd, J = 17.2, 10.4, 6.2 Hz, 1H), 5.28-5.15 (m, 3H), 4.50 (bs, 2H), 3.48 (t, J = 6.4 Hz, 2H), 2.06 (s, 3H), 1.75-1.60 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.3, 138.4, 136.3, 128.3, 127.6, 127.5, 116.7, 74.5, 72.9, 69.8, 30.8, 25.4, 21.2; IR (neat, cm^{-1}) 3087.8, 3063.9, 3031.2, 2940.3, 2857.9, 1737.7, 1647.0, 1496.0, 1454.1; HRMS (ESI) m/z calculated for $C_{15}H_{20}O_3Na$ [$M + Na$] $^+$: 271.1310; found: 271.1302.

This material was then subjected to the standard procedure for cleavage of the allylic acetate which afforded allylic alcohol (\pm)-**3** ready for subsequent resolution: Run 1: 185 mg, 0.897 mmol, 99% yield, [B:L] = 4.7:1. Run 2: 181 mg, 0.877 mmol, 99% yield; [B:L] = 3.8:1

4.2.2.2 Methyl (9R)-9-acetoxyundec-10-eneoate 9-OAc: The general procedure for the asymmetric branched allylic oxidation afforded: Run 1: 235 mg, 0.915 mmol, 92% yield, [B:L] = 5.1:1, [ee] = 58%. Run 2: 224 mg, 0.876 mmol, 88% yield; [B:L] = 4.3:1, [ee] = 55%. Run 3 (**gram scale**): 1.09 g, 4.250 mmol, 85% yield; [B:L] = 4.1:1, [ee] = 57%. (β -cyclodextrin, 120°C isothermal, $t_R(R)$ = 55.96 min., $t_R(S)$ = 57.30 min.), [average yield:

90%]; This material was taken forward without further purification. **¹H NMR** (500 MHz, CDCl₃) δ 5.78 (ddd, *J* = 17.1, 10.5, 6.5 Hz, 1H), 5.24-5.14 (m, 3H), 3.66 (s, 3H), 2.29 (t, *J* = 8.0 Hz, 2H), 2.05 (s, 3H), 1.62-1.53 (m, 4H), 1.29 (bs, 8H); **¹³C NMR** (125 MHz, CDCl₃) δ 174.2, 170.3, 136.5, 116.5, 74.8, 51.4, 34.1, 34.0, 29.1, 29.0, 29.0, 24.9, 24.8, 21.2; **IR** (neat, cm⁻¹) 3089.1, 2932.9, 2858.2, 1742.0, 1436.3, 1371.5; **HRMS** (ESI) *m/z* calculated for C₁₄H₂₄O₄Na [M + Na]⁺: 279.1572; found: 279.1564.

This material was then subjected to the standard procedure for cleavage of the allylic acetate which afforded allylic alcohol (±)-**9** ready for subsequent resolution: Run 1: 188 mg, 0.877 mmol, 96% yield, [B:L] = 5.1:1. Run 2: 179 mg, 0.835 mmol, 95% yield; [B:L] = 4.3:1. Run 3 (gram scale): 879 mg, 4.101 mmol, 96% yield; [B:L] = 4.1:1

4.2.2.3 2-((3R)-Pent-3-acetoxy-4-en-1-yl-3-ol)-1,3-dioxane 13-OAc: Following the general procedure for the asymmetric branched allylic oxidation afforded: Run 1: 180 mg, 0.840 mmol, 84% yield; [B:L] = 4.8:1:1, [ee] = 44%. Run 2: 178 mg, 0.831 mmol, 83% yield; [B:L] = 4.3:1, [ee] = 46%. (β-cyclodextrin, 110°C isothermal, *t_R*(R) = 22.21 min., *t_R*(S) = 22.79 min.), [average yield: 84%.]; This material was taken forward without further purification. **¹H NMR** (500 MHz, CDCl₃) δ 5.76 (ddd, *J* = 6.5, 10.5, 17.3 Hz, 1H), 5.24 (q, *J* = 6.5 Hz, 1H), 5.23 (dm, *J* = 17.5 Hz, 1H), 5.16 (dm, *J* = 10.5 Hz, 1H), 4.53 (t, *J* = 5.0 Hz, 1H), 4.09 (m, 2H), 3.75 (dt, *J* = 3.0, 12.5 Hz, 2H), 2.12-2.02 (m, 1H), 2.06 (s, 3H), 1.78-1.58 (m, 4H), 1.33 (dm, *J* = 13.5 Hz, 1H); **¹³C NMR** (125 MHz, CDCl₃) δ 170.2, 136.3, 116.7, 101.7, 74.3, 66.9, 30.7, 28.5, 25.8, 21.1; **IR** (neat, cm⁻¹) 3087.5, 2962.1, 2931.3, 2852.2, 2780.9, 2732.7, 2661.3, 1739.5, 1646.9, 1430.9, 1407.8; **HRMS** (ESI) *m/z* calculated for C₁₁H₁₈O₄Na [M+Na]⁺: 237.1103; found 237.1104.

This material was then subjected to the standard procedure for cleavage of the allylic acetate which afforded allylic alcohol (±)-**13** ready for subsequent resolution: Run 1: 141 mg, 0.819 mmol, 97% yield, [B:L] = 4.8:1. Run 2: 135 mg, 0.784 mmol, 94% yield; [B:L] = 4.3:1

4.2.2.5 (4R, E)-Methyl 4-acetoxy-6-phenylhex-5-enoate (18): The general procedure for the asymmetric branched allylic oxidation was modified in the following way to generate allylic acetate (**18**). A round bottom flask (25 mL) was charged with the following: 1,2-Bis(phenylsulfinyl)ethane palladium(II) acetate (**1**) (10 mol%, 0.50 mmol, 250 mg); (1*R*, 2*R*)-(–)-[1,2-Cyclohexanediamino-*N,N'*-bis(3,5-di-*t*-butylsalicylidene)] Chromium(III)F(*R,R*-**2**) (10 mol%, 0.50 mmol, 308 mg), 1,4-benzoquinone (2 equiv., 10.0 mmol, 1.08 g), an activated 4Å MS bead (~30 mg), and a Teflon© stir bar. A separate vial (2 mL, borosilicate) was charged with the following: Methyl hexenoate (1.0 equiv, 5.0 mmol, 0.704 mL), AcOH (1.1 equiv., 5.5 mmol, 0.315 mL), and EtOAc (0.50 mL). The liquids were transferred to the solids via pipette and the vial rinsed with EtOAc (4 × 0.50 mL). After carefully stirring for 48 hrs at room temperature, to the reaction was added phenyl boronic acid (1.5 equiv., 7.5 mmol, 0.914 g), AcOH (1 equiv., 5 mmol, 0.285 mL), and EtOAc (12.5 mL). The reaction was stirred at room temperature until complete by TLC (~4 hr) at which point the reaction mixture was transferred to a separatory funnel with ~5 mL EtOAc and diluted with hexanes (400 mL). The organic layer was rinsed with sat. aq. NaHSO₃ (1 × 50 mL) and 5% aq. K₂CO₃ (2 × 50 mL). Caution should be taken when combining aqueous layers as carbon dioxide is evolved. The combined aqueous layers were

back extracted with hexanes (100 mL). The combined organic layers were dried (MgSO_4), filtered, and reduced *in vacuo*. The resulting oil was re-dissolved in hexanes (150 mL) and extracted again with 5% aq. K_2CO_3 (3×25 mL) to remove residual hydroquinone. The organic layer was again dried (MgSO_4), filtered and reduced *in vacuo*. This product was generally taken forward without further purification, but was isolated and purified via silica gel chromatography for characterization. [B:L] = >20:1, [ee] = 50%. (Determined on the initial branched acetate product prior to oxidative Heck reaction, β -cyclodextrin, 110°C isothermal, $t_{\text{R}}(\text{R}) = 5.52$ min., $t_{\text{R}}(\text{S}) = 5.83$ min.), $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.39 (d, $J = 7.5$ Hz, 2H), 7.34 (t, $J = 7.5$ Hz, 2H), 7.31-7.25 (m, 1H), 6.64 (d, $J = 16.0$ Hz, 1H), 6.12 (dd, $J = 7.5, 15.8$ Hz, 1H), 5.46 (q, $J = 6.5$ Hz, 1H), 3.68 (s, 3H), 2.42 (dt, $J = 2.0, 7.8$ Hz, 2H), 2.13-2.07 (m, 2H), 2.10 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 173.2, 170.2, 136.0, 133.0, 128.5, 128.0, 126.7, 126.6, 73.7, 51.7, 29.8, 29.5, 21.2; **IR** (neat, cm^{-1}) 3085.6, 3025.8, 2952.5, 2848.4, 1737.6, 1658.5, 1598.7, 1597.4, 1494.6; **HRMS** (ESI) m/z calculated for $\text{C}_{15}\text{H}_{18}\text{O}_4\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 285.1103; found 285.1092.

4.2.3 General procedure for resolution with Novozyme 435—To a flame dried round bottom flask containing allylic alcohol to be resolved (1 equiv.) was added vinyl acetate (0.6 M) and Novozyme 435 immobilized on polystyrene beads (33.3 mg/1 mmol). The reaction was stirred vigorously at room temperature for 36 hrs. Upon completion, the solid supported enzyme was removed via filtration. The solid support was rinsed thoroughly with diethyl ether and then the filtrate reduced *in vacuo* and purified via standard SiO_2 chromatography. Enantioselectivities were determined by chiral gas chromatographic analysis on the acetylated derivative of each isolated alcohol. It was found that the recovered solid supported enzyme could be used up to 5 times with little diminishment in activity. Individual yields and selectivities are reported below.

4.2.3.1 (–)-(4R)-1-O-Benzyl-5-hexen-1,4-diol (–)-3: Following the general procedure for Novozyme 435 resolution afforded: Run 1: 105 mg, 0.509 mmol, 57% yield, [B:L] = >20:1, [ee] = 98%. Run 2: 100 mg, 0.485 mmol, 55% yield; [B:L] = >20:1, [ee] = 99%. Enantiomeric excess was determined on the acylated derivative of the final product (ee determined on the acylated alcohol, β -cyclodextrin, 120°C isothermal, $t_{\text{R}}(\text{R}) = 65.56$ min., $t_{\text{R}}(\text{S}) = 67.14$ min), [average yield: 56%]; [α] $^{26}_{\text{D}}$ = -2.86° ($c = 2.0$, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.37-7.32 (m, 4H), 7.30-7.25 (m, 1H), 5.87 (ddd, $J = 17.0, 10.5, 6.0$ Hz, 1H), 5.25 (dt, $J = 17.0, 1.5$ Hz, 1H), 5.10 (dt, $J = 10.5, 1.5$ Hz, 1H), 4.52 (s, 2H), 4.13 (m, 1H), 3.52 (t, $J = 6.0$ Hz, 2H), 2.27 (d, $J = 4.5$ Hz, 2H), 1.77-1.57 (m, 4H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 141.0, 138.1, 128.3, 127.6, 127.6, 114.4, 72.9, 72.6, 70.2, 34.2, 25.7; **IR** (neat, cm^{-1}) 3403.8, 3066.3, 3031.6, 2979.5, 2942.9, 2858.0, 2798.2, 1643.1, 1496.5, 1454.1; **HRMS** (ESI) m/z calculated for $\text{C}_{14}\text{H}_{24}\text{O}_2\text{Na}$ [$\text{M}+\text{Na}$] $^+$: 229.1204; found: 229.1204.

4.2.3.2 Methyl (9R)-9-hydroxyundec-10-enoate (–)-9: Following the general procedure for Novozyme 435 resolution afforded: Run 1: 119 mg, 0.555 mmol, 63% yield, [B:L] = >20:1, [ee] = 99%. Run 2: 109 mg, 0.509 mmol, 61% yield; [B:L] = >20:1, [ee] = 98%, Run 3 (gram scale): 523 mg, 2.441 mmol, 60% yield; [B:L] = >20:1, [ee] = 99%. (ee determined on the acylated alcohol, β -cyclodextrin, 120°C isothermal, $t_{\text{R}}(\text{R}) = 55.92$ min.), [average

yield: 62%]; $[\alpha]_D^{25} = -5.13^\circ$ ($c = 1.0$, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 5.86 (ddd, $J = 16.9, 10.8, 6.0$ Hz, 1H), 5.22 (d, $J = 17.0$ Hz, 1H), 5.10 (d, $J = 10.5$ Hz, 1H), 4.09 (p, $J = 5.5$ Hz, 1H), 3.66 (s, 3H), 2.30 (t, $J = 7.5$ Hz, 2H), 1.63 – 1.30 (m, 13H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 174.2, 141.3, 114.4, 73.2, 51.4, 37.0, 34.1, 29.3, 29.1, 29.0, 25.2, 24.9; **IR** (neat, cm^{-1}) 3426.9, 2979.5, 2931.3, 2856.1, 1739.5, 1436.7; **HRMS** (ESI) m/z calculated for $\text{C}_{12}\text{H}_{22}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 237.1467; found: 237.1471.

4.2.3.3 2-((3R)-Pent-4-en-1-yl-3-ol)-1,3-dioxane (-)-13: Following the general procedure for Novozyme 435 resolution afforded: Run 1: 80 mg, 0.464 mmol, 57% yield; [B:L] = >20:1:1, [ee] = 99%. Run 2: 76 mg, 0.441 mmol, 56% yield; [B:L] = >20:1, [ee] = 99%. (ee determined on the acylated alcohol, β -cyclodextrin, 110°C isothermal, $t_R(\text{R}) = 22.31$ min., $t_R(\text{minor}) = 22.93$ min.), [average yield: 57%.]; $[\alpha]_D^{24} = -5.01^\circ$ ($c = 1.0$, CHCl_3); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 5.86 (ddd, $J = 5.6, 10.4, 17.3$ Hz, 1H), 5.24 (dt, $J = 1.6, 17.2$ Hz, 1H), 5.10 (dt, $J = 1.2, 10.8$ Hz, 1H), 4.58 (t, $J = 4.4$ Hz, 1H), 4.18-4.08 (m, 3H), 3.77 (app t, $J = 11.6$ Hz, 2H), 2.36 (d, $J = 4.0$ Hz, 1H), 2.08 (qt, $J = 4.0, 12.4$, 1H), 1.78-1.58 (m, 4H), 1.35 (d sep, $J = 1.2, 13.6$ Hz, 1H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 141.0, 114.4, 102.1, 72.6, 66.9, 31.2, 31.1, 25.7; **IR** (neat, cm^{-1}) 3430.8, 3079.8, 2962.1, 2929.4, 2856.1, 2734.6, 1643.1, 1429.0, 1405.9; **HRMS** (ESI) m/z calculated for $\text{C}_9\text{H}_{16}\text{O}_3\text{Na}$ $[\text{M}+\text{Na}]^+$: 195.0995; found 195.0997.

4.2.4 General procedure for resolution with Subtilisin. Carlsberg—The active enzyme for resolution was prepared as previously described by Boren and co-workers.¹⁵ To a flame dried round bottom flask containing allylic alcohol to be resolved (1 equiv.) was added isoproenyl valerate (1.5 equiv), active S. Carlsberg (36 mg/1 mmol), sodium carbonate (1 equiv.) and THF (0.5 M). The reaction was stirred vigorously at room temperature for 60 hrs. Upon completion, the enzyme was removed via filtration. The enzyme was rinsed thoroughly with diethyl ether and then the filtrate reduced *in vacuo* and purified via standard SiO_2 chromatography. Enantioselectivities were determined by chiral gas chromatographic analysis on the acetylated derivative of each isolated alcohol. Individual yields and selectivities are reported below.

4.2.4.1 (+)-(4S)-1-O-Benzyl-5-hexen-1,4-diol (+)-3: Material for this route was obtained by application of the general ABAO procedure using (*S,S*)-**2** as a chiral catalyst. Subsequent acetate deprotection by the general procedure described afforded: Run 1: 180 mg, 0.873 mmol, 87% yield; [B:L] = 4.4:1, [ee] = 46%. Run 2: 187 mg, 0.906 mmol, 91% yield; [B:L] = 4.1:1, [ee] = 45%. Yields and selectivities are over two-steps. This material was then subjected to the general procedure for resolution with S. Carlsberg to afford chiral allylic alcohol: Run 1: 92 mg, 0.446 mmol, 52% yield, [B:L] = >20:1, [ee] = 99%. Run 2: 97 mg, 0.470 mmol, 54% yield; [B:L] = >20:1, [ee]; Enantiomeric excess was determined on the acylated derivative of the final product (ee determined on the acylated alcohol, β -cyclodextrin, 120°C isothermal, $t_R(\text{S}) = 67.03$ min) [average yield: 53%.]; $[\alpha]_D^{26} = +2.85^\circ$ ($c = 2.0$, CHCl_3).

4.2.5 Synthesis of furan core (-)-22

4.2.5.1 (R, E)-5-styryldihydrofuran-2(3H)-one (19): To crude **18** (5 mmol, assumed) in a round bottom flask (250 mL) was added THF (18.75 mL), DI H₂O (6.25 mL), and a Teflon[®] stir bar. The flask was cooled to 0°C and LiOH·H₂O (0.623 g, 15 mmol, 3.0 equiv.) was added in one portion. The ice bath was removed after 10 minutes and the reaction monitored via TLC. Upon completion (~2-4 hr) benzene (150 mL) was added and the flask was transferred to a 100°C oil bath and a Dean-Stark trap and a reflux condenser were added. The reaction was brought to a comfortable reflux and then allowed to stir overnight. After removing the flask from the bath and allowing it to cool to room temperature, the contents were transferred to a separatory funnel and the organic layer washed with aq. 1M H₃PO₄ (3 × 25 mL). The organic layer was then dried (MgSO₄), filtered, and reduced *in vacuo*. The resulting off white solid was purified via silica gel chromatography (10-30% Et₂O:Hexanes) to afford a white solid. (0.504 g, 2.678 mmol, 54% (2-step)) ¹H NMR (500 MHz, CDCl₃) δ 7.40 (d, *J* = 7.5 Hz, 2H), 7.37-7.32 (m, 2H), 7.30-7.26 (m, 1H), 6.69 (d, *J* = 16.0 Hz, 1H), 6.21 (dd, *J* = 6.5, 16.0 Hz, 1H), 5.13 (q, *J* = 6.5 Hz, 1H), 2.65-2.54 (m, 2H), 2.50 (app sextuplet, *J* = 9.0 Hz, 1H), 2.11 (ddd, *J* = 9.0, 12.5, 16.6 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 176.9, 135.6, 132.9, 128.7, 128.4, 126.7, 126.4, 80.5, 28.8, 28.5; IR (neat, cm⁻¹) 2989.1, 2950.6, 1762.6, 1722.1, 1454.1, 1415.5; HRMS (ESI) *m/z* calculated for C₁₂H₁₃O₂ [M+H]⁺: 189.0916; found 189.0918.

4.2.5.2 (R)-5-((4R,5R)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl)dihydrofuran-2(3H)-one ((-)-20): To a clean, dry 100 mL recovery flask was added sequentially the following: K₂OsO₄ · 2H₂O (0.018 g, 0.05 mmol, 1 mol%), (DHQD)₂PHAL (0.199 g, 0.25 mmol, 5 mol %), K₃Fe(CN)₆ (4.94 g, 15 mmol, 3 equiv.), K₂CO₃ (2.07 g, 15 mmol, 3 equiv.), NaHCO₃ (1.34 g, 15 mmol, 3 equiv.), a Teflon[®] stir bar, deionized water (24 mL), and tert-butanol (24 mL). The reaction flask was stirred vigorously until both layers became translucent, at which time MeSO₂NH₂ (0.476 g, 5 mmol, 1 equiv.) was added and the reaction was cooled to 0°C. After the solution became opaque, olefin (**19**) (0.941 g, 5 mmol, 1 equiv.) was added in one portion. CH₂Cl₂ (2.4 mL) was added to improve SM solubility and the reaction was stirred vigorously at 0°C for 1 hr, then warmed to room temperature and stirred until completion as indicated by TLC (~5 hr). Upon completion, sodium bisulfite (2 g) was added slowly and the reaction stirred for 1 hour. The reaction mixture was transferred to a separatory funnel and EtOAc (50 ml) was added. The aqueous layer was extracted with additional EtOAc (3 × 50 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated *in vacuo*. To the crude diol was added DMF (8.4 mL, 0.6 M) and 2-methoxypropene (4.79 mL). The reaction was cooled to 0°C and *p*-TsOH·H₂O (0.238 g, 1.25 mmol, 0.25 equiv.) was added and the reaction allowed to warm to room temperature while stirring overnight. The reaction mixture was then transferred to a separatory funnel and diluted with Et₂O (200 mL). The organic layer was washed with DI H₂O (3 × 25 mL) and brine (1 × 25 mL). The organic layer was then dried (MgSO₄), filtered, and reduced *in vacuo*. Residual DMF or 2-methoxypropene was removed by addition of benzene and *in vacuo* concentration. The crude oil was purified by silica gel chromatography in 10-40% Et₂O:Hexanes to afford a white solid (0.920 g, 3.52 mmol, 70% yield (2-step), >20:1 dr, 99% ee (Determined on Chiracel AD-RH, 35:75 CH₃CN:H₂O, *t*_R(major) = 7.3 min., *t*_R(minor) = 6.8 min.) [α]_D²⁶ = -94.9° (c = 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ

7.39-7.31 (m, 5H), 4.78 (d, $J = 8.5$ Hz, 1H), 4.60 (ddd, $J = 4.0, 6.3, 7.5$ Hz, 1H), 4.10 (dd, $J = 4.0, 8.3$ Hz, 1H), 2.60 (ddd, $J = 6.5, 10.0, 18.0$ Hz, 1H), 2.51 (ddd, $J = 7.5, 9.5, 17.4$ Hz, 1H), 2.38-2.24 (m, 2H), 1.56 (s, 3H), 1.52 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 176.5, 137.2, 128.8, 128.7, 126.7, 110.2, 83.4, 80.1, 78.7, 28.1, 27.1, 27.0, 22.9; **IR** (neat, cm^{-1}) 3066.3, 3031.6, 2985.3, 2935.1, 2980.8, 1781.9, 1604.5, 1494.6, 1456.0; **HRMS** (ESI) m/z calculated for $\text{C}_{12}\text{H}_{22}\text{O}_4$ $[\text{M}+\text{H}]^+$: 263.1283; found 263.1280. The absolute configuration of this molecule was determined on a crystal grown from benzene of *p*-bromophenyl-**20** synthesized through the same sequence. The cif file for this compound can be found as an additional file of the supporting information.

4.2.5.3 (R)-5-((4R,5R)-2,2-dimethyl-5-phenyl-1,3-dioxolan-4-yl)furan-2(5H)-one

(+)-21—To a clean, flame dried 25 mL recovery flask charged with a Teflon stir bar and under an argon atmosphere was added THF (5 mL) and hexamethyldisilazane (1.36 mmol, 0.288 mL, 1.1 equiv.). The reaction was cooled to -78°C , and *n*-Buli (1.30 mmol, 0.813 mL, 1.05 equiv.) was added dropwise via syringe. After stirring for ten minutes, (–)-**20** (1.24 mmol, 0.325 g, 1 equiv.) in THF (1 mL, 0.15 mL rinse) was added slowly via cannula. The reaction was stirred a further 25 minutes, and then phenylselenenyl bromide (1.24 mmol, 0.293 g, 1 equiv.) in THF (1.15 mL) was added via cannula over ~10 min. The reaction was stirred for an additional 5 minutes and then quenched at -78°C with 1N HCl (5 mL). The reaction mixture was transferred to a separatory funnel and diluted with Et_2O (200 mL). The organic layer was washed with sat. aq. NaHCO_3 (2×10 mL). The organic layer was then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Reproducibility for the elimination step was significantly improved by quickly purifying away fast running selenium containing species by SiO_2 chromatography in 5%-10%-20% Et_2O :Hexanes. To the mixture of selenides (1.03 mmol, 0.425 g, 1 equiv.) in a clean, dry 100 mL flask was added CH_2Cl_2 (20.6 mL, 0.05 M) and the reaction flask was cooled to 0°C in an ice bath. Hydrogen peroxide (3.08 mmol, 0.346 mL of 30% solution, 3 equiv.) was then added slowly via syringe. The reaction was stirred at 0°C and conversion monitored by TLC. Upon completion, the reaction mixture was transferred to a separatory funnel and CH_2Cl_2 was added (200 mL). The organic layer was then washed with DI H_2O (2×20 mL) and brine (20 mL). The organic layer was then dried (MgSO_4), filtered, and reduced *in vacuo*. The crude oil was purified by silica gel chromatography in 10-40% Et_2O :Hexanes to afford a white solid (0.237 g, 0.91 mmol, 73% yield (2-step)). $[\alpha]_D^{25} = 555.6^\circ$ ($c = 1.0$, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 7.48 (dd, $J = 1.5, 6.0$ Hz, 1H), 7.40-7.31 (m, 5H), 6.17 (dd, $J = 2.5, 5.8$ Hz, 1H), 5.16 (dt, $J = 2.0, 6.5$ Hz, 1H), 5.02 (d, $J = 8.0$ Hz, 1H), 3.91 (dd, $J = 6.5, 7.5$ Hz, 1H), 1.56 (s, 3H), 1.54 (s, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 172.2, 153.8, 137.3, 128.6, 128.6, 127.0, 122.6, 110.6, 82.8, 82.7, 80.7, 27.1, 26.8; **IR** (neat, cm^{-1}) 3089.4, 3033.5, 2989.1, 2935.1, 2894.6, 1783.8, 1758.8, 1602.6, 1496.5, 1456.0; **HRMS** (ESI) m/z calculated for $\text{C}_{15}\text{H}_{17}\text{O}_4$ $[\text{M}+\text{H}]^+$: 261.1127; found 263.1123.

4.2.5.4 (3aS,5R,6S,6aS)-6-hydroxy-5-phenyltetrahydrofuro[3,2-b]furan-2(5H)-one(–)-22

(–)-22—To (+)-**21** (0.91 mmol, 0.237 g, 1 equiv.) in a clean, dry round bottom flask (50 mL) with a Teflon© stir bar was added THF (9.1 mL) and 1N HCl (5-10 drops). The reaction mixture was heated to 45°C and monitored via TLC (70% EtOAc :Hex). Deprotection and cyclization would generally proceed to completion under these conditions

with prolonged stirring, but could be expedited by the following procedure. After complete acetonide deprotection by TLC, the flask was cooled to 0°C and CH₂Cl₂ (9.1 mL) and NEt₃ was added until a pH of ~10 was obtained. The flask was then allowed to warm to room temperature and monitored via TLC. Upon completion (~4-6 hr), the contents were transferred to a separatory funnel and diluted with further CH₂Cl₂. The organic layer was then washed with sat. aq. NH₄Cl solution (3 × 15 mL). The combined aqueous layers were back extracted with EtOAc (3 × 50 mL) and then the combined organic layers were dried (MgSO₄), filtered, and reduced *in vacuo*. The resulting off white solid was purified via silica gel chromatography (10-50% EtOAc:Hexanes) to afford a white solid. (0.161 g, 0.731 mmol, 80%) [α]_D²⁶ = -17.1° (c = 1.0, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 7.44-7.34 (m, 5H), 5.23 (d, *J* = 2.5 Hz, 1H), 5.20 (td, *J* = 1.0, 5.0 Hz, 1H), 5.07 (d, *J* = 5.0 Hz, 1H), 4.64 (app t, *J* = 2.0 Hz, 1H), 2.86 (dd, *J* = 6.0, 18.8 Hz, 1H), 2.79 (d, *J* = 18.5 Hz, 1H), 1.36 (d, *J* = 2.5 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 175.4, 134.2, 128.9, 128.6, 126.6, 87.2, 82.8, 77.1, 75.8, 36.0; IR (neat, cm⁻¹) 3948.3, 2975.6, 2948.6, 2923.6, 2858.0, 1766.5, 1496.49, 1454.1; HRMS (ESI) *m/z* calculated for C₁₂H₁₂O₄Na [M+Na]⁺: 243.0645; found 243.0633.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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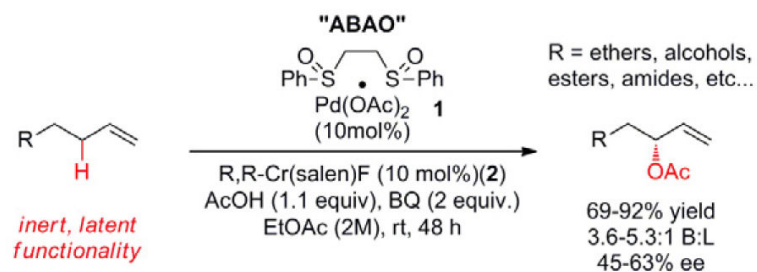
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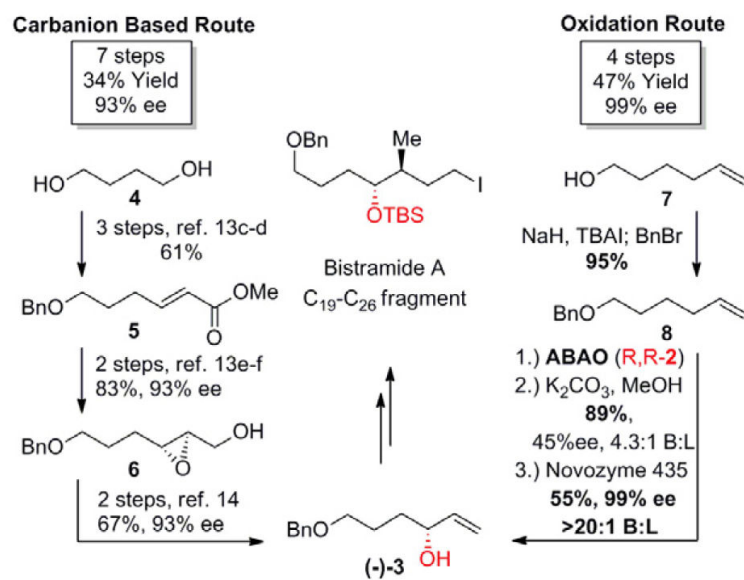
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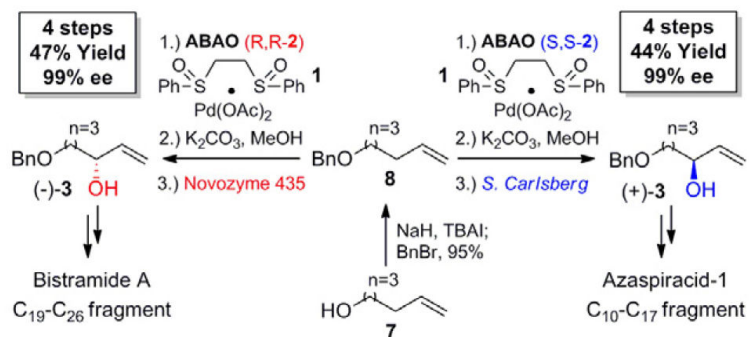
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**Scheme 1.**

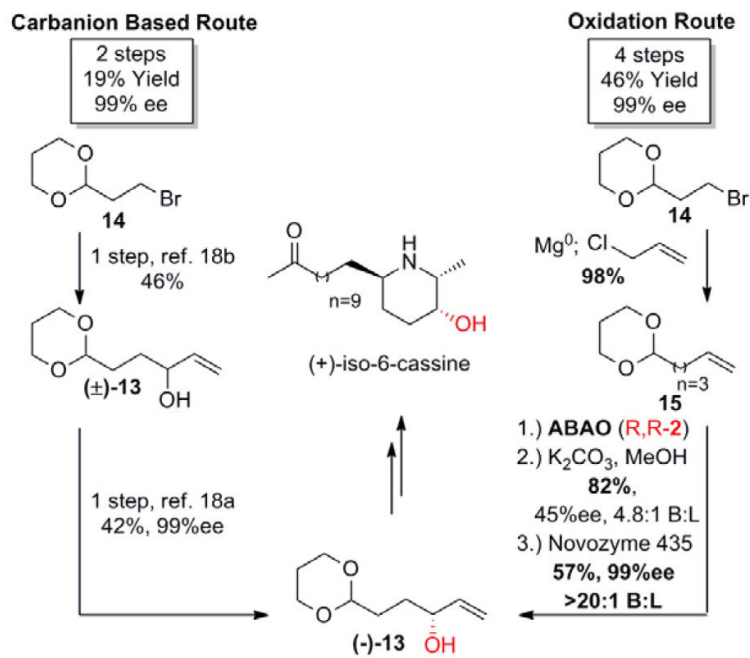
The asymmetric branched allylic oxidation reaction. R,R-Cr(Salen)F = (R,R)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminochromium (III) fluoride

**Scheme 2.**

C-H oxidation vs carbanion based route to (-)-**3**, a precursor of the C₁₉-C₂₆ fragment of Bistramide A

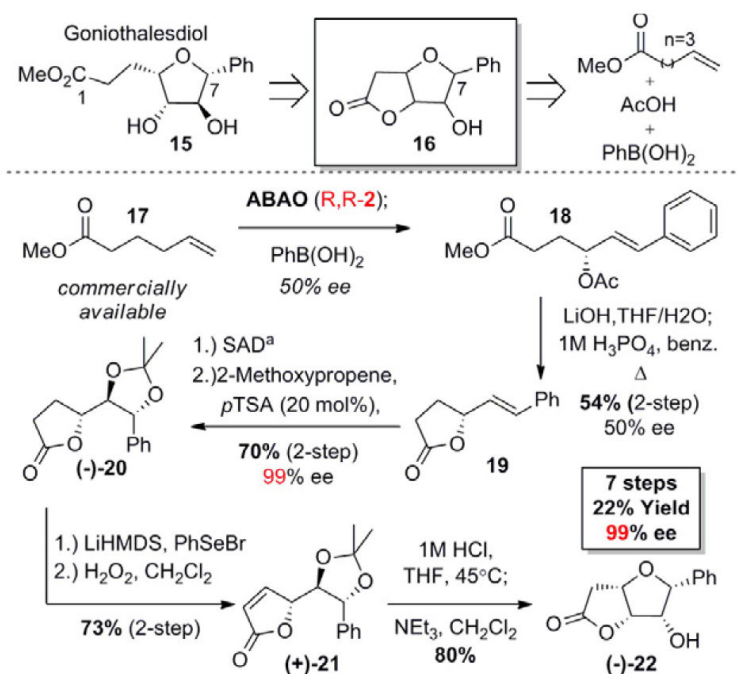


Scheme 3.
 Stereoselective C–H oxidation approach to each enantiomer of allylic alcohol 3



Scheme 5.

C–H Oxidation vs. carbanion based route for the synthesis of (+)-*iso*-6-cassine precursor (-)-13

**Scheme 6.**

Enantioselective C–H oxidation approach to the core furan precursor (–)-**22** of the goniathalesdiol family. ^aSAD = Sharpless Asymmetric Dihydroxylation. Conditions: K₂OsO₄·2H₂O (1 mol%), (DHQD)₂PHAL (5 mol%), K₂CO₃ (3 equiv.), NaHCO₃ (3 equiv.) K₃Fe(CN)₆ (3 equiv.), MeSO₂NH₂ (1 equiv.), t-BuOH:H₂O:CH₂Cl₂ 10:10:1, 0°C→rt