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The Enantioselective Construction of Tetracyclic Diterpene Skeletons with Friedel-Crafts Alkylation and Palladium-catalyzed Cycloalkenylation Reactions

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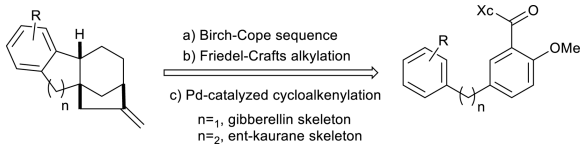
Abstract



Due to the profound extent to which natural products inspire medicinal chemists in drug discovery, there is demand for innovative syntheses of these often complex materials. This article describes the synthesis of tricarbocyclic natural product architectures through an extension of the enantioselective Birch-Cope sequence with intramolecular Friedel-Crafts alkylation reactions. Additionally, palladium-catalyzed enol silane cycloalkenylation of the tricarbocyclic structures afforded the challenging bicyclo[3.2.1]octane C/D ring system found in the gibberellins and the ent-kauranes, two natural products with diverse medicinal value. In the case of the ent-kaurane derivative, an unprecedented alkene rearrangement converted four alkene isomers to one final product.

Introduction

Natural product structures continue to inspire synthetic chemists and drug developers alike with their complex molecular architecture that frequently exceeds human imagination. More importantly, these fascinating structures often possess useful and unique biological activities that inspire new therapeutic approaches[1–5]. Gibberellin[6] and *ent*-kaurane derivatives[7, 8] are two diterpene natural products[9] with a complex tetracyclic molecular architecture (Figure 1) featuring, most prominently, a bicyclo[3.2.1]octane system, which has been the focus of significant recent synthetic efforts[10, 11]. Both gibberellins and *ent*-kauranes have noteworthy biological activity; the gibberellins as plant hormones and growth regulators[12–14], and the *ent*-kauranes in a wide array of therapies. In fact, recent therapeutic applications of *ent*-

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Electronic supplementary information available. Copies of ^{1}H and ^{13}C NMR spectra, gas chromatographs and mass spectra for all new compounds.

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kauranes include anti-inflammation[15], anti-HIV[16], antibacterial[17], anti-tuberculosis[18], and anti-cancer[19–23]. Clearly these molecular architectures have promising potential value.

Although both gibberellins and *ent*-kauranes have members that are commercially available, the *de novo* construction of their structures can facilitate derivatization and potentially more active analogs. Since the 1970's, there has been considerable synthetic effort aimed at the *de novo* construction of both frameworks, although there has been much less enantioselective work. Enantioselective *de novo* syntheses of gibberellins include two impressive works in 1981 by Takano[24, 25] and one by Corey in 1991[26]. Enantioselective *de novo* syntheses of the *ent*-kauranes include two works by Corey in 1997[27, 28], Toyota in 2000[29], and Reisman in 2013[30, 31].

At the core of both the gibberellins and the *ent*-kauranes is a tetracarbocyclic ring system that creates significant synthetic challenges, including an all-carbon quaternary stereocenter. We hypothesized that the tetracyclic ring system might be accessible from a properly designed product of our previously reported Birch-Cope sequence[32]. We have illustrated applications of the Birch-Cope sequence products in the enantioselective synthesis of two alkaloids, (−)-lycoramine[33] and (+)-mesembrine[34]. An enantioselective approach to the diterpene frameworks of gibberellins or *ent*-kauranes would expand the potential applications in natural product-like molecule synthesis. To that end, we fashioned the retrosynthetic plan shown in Scheme 1, in which the tetracarbocyclic core of these valuable compounds is generated with just two additional steps after the Birch-Cope sequence: a Friedel-Crafts alkylation and a palladium-catalyzed cycloalkenylation. The final product would contain the carbon skeleton of the gibberellins or *ent*-kauranes depending on the length of the linker between the two diaryl rings of the Birch-Cope sequence starting material. In the process, the strategy would create ring D and the bicyclo[3.2.1]octane at a later stage, after rings A-C have been generated. To the best of our knowledge, this approach has not previously been used with the palladium-catalyzed cycloalkenylation[35–38]. The Friedel-Crafts alkylation would rely on precedent[39–43] and would be the second example of an intramolecular carbon nucleophile conjugate addition to the enone system of the Birch-Cope sequence product; along with the Rauhut-Currier reaction that we have recently communicated[44, 45]. In combination, the two steps would be a relatively short enantioselective entry to two natural product-like scaffolds.

Results and Discussion

Construction of the Diaryl Starting Materials

The first stage of the process to generate gibberellin or *ent*-kaurane carbon skeletons involved synthesizing the Birch-Cope sequence reactants. We previously used cross-coupling chemistry in our synthesis of (−)-lycoramine and (+)-mesembrine to make biaryl reactants, but the diaryl materials with methane or ethane linkers required for this work would, at first glance, seem to necessitate the much less common cross-coupling reaction of an sp^2 carbon with an sp^3 carbon. Therefore, we initially explored the synthesis of the diarylmethane substrates through Grignard reagent nucleophilic additions to benzaldehyde derivatives followed by reduction of the resulting diaryl alcohol. These efforts were successful, but not without some complications (e.g. magnesium-Oppenhauer oxidation side

reactions[46]) and eventually proved less expedient than a cross-coupling approach. In particular, Suzuki reaction of the 5-iodo-salicylate derivative **1**[34] (Table 1) with benzyl boronic acid derivatives[47] in the presence of catalytic $Pd_2(dba)_3$ rapidly afforded the diaryl substrates **2** with a methane linker, albeit with some modest yields. Benzylboronic pinacol ester is commercially available and the four other aryl substituted derivatives were synthesized following literature protocols[48] in one step from the appropriately substituted benzyl bromide, stoichiometric magnesium and pinacolborane.

To leverage the facility of sp^2-sp^2 cross-coupling reactions and avoid the beta-hydride elimination complications introduced by a phenylethane cross-coupling partner, the ethane linked diaryl substrates were synthesized through a two-step process: Heck reaction of **1** with an appropriate styrene analog and subsequent hydrogenation of the resulting stilbene derivative (Table 2). Styrene worked efficiently with N,N-dimethyl-β-alanine as the ligand, but the same alanine ligand afforded low yields with the more electron rich styrene derivative in the synthesis of **3b**. After some experimentation, the optimal Heck reaction conditions were found with the ligandless palladium conditions of Botella[49]. As can be seen in Table 2, both steps of the process were quite efficient for a range of substrates.

Birch-Cope sequence

Subjecting the methane- and ethane-linked diaryl substrates, **2** and **4**, to the Birch-Cope sequence began with the enantioselective Birch reduction-allylation, which afforded products **5** and **6** in moderate to very good yields (Table 3). As has been demonstrated before[32, 33], the Birch reduction is selective for the more electron deficient aryl ring. The enantioselectivity of the Birch reduction-alkylation has been demonstrated on many previous occasions[32–34, 51, 52] and was confirmed to afford an enantiomeric ratio of 24:1 for **4d** in the current work (see Supporting Information). Note that the natural enantiomers of the gibberellins and *ent*-kauranes would be generated from the use of D-prolinol as a chiral auxiliary (X_c), however L-prolinol was used for this exploratory work to reduce costs while still illustrating the feasibility of the process. The Birch products, **5** and **6**, were purified, but they decomposed over time so they were immediately taken through the next two steps of the Birch-Cope sequence. In that event, hydrolysis of the enol ether and stereoselective Cope rearrangement provided **9** and **10**. Like prior analogs[32, 34], the Cope rearrangement favors the more thermodynamically stable conjugated enone and the reduction in steric congestion around the C-2 position of the cyclohex-3-enones **7** and **8**. Although all of these substrates were new examples in the Birch-Cope sequence, they demonstrated similar efficiency as previously reported examples with aryl or alkyl groups in the C-4 position.

Intramolecular Friedel-Crafts alkylation

Elaboration of these Birch-Cope sequence products, **9** and **10**, into the tetracarbocyclic framework of the gibberellins or the *ent*-kauranes began by the construction of the central B ring through a Friedel-Crafts alkylation. A standard selection of Lewis acids were screened including $AlCl_3$, $TiCl_4$, and $SnCl_4$, but $BF_3{\cdot}Et_2O$ was clearly the best at coaxing the conjugate addition of the aromatic nucleophile to add to the cyclohexenone electrophile[40–43]. The cyclization occurred to form the cis isomers **11** and **12**, but most of the products were isolated as C-2 epimers, typically a 1:1 mixture. Subsequent cleavage of

the chiral auxiliary (vide infra) confirmed this observation by affording one enantiomerically pure product, thus dispelling the possibility of epimers at the C-3 bridgehead position. As anticipated, the intramolecular Friedel-Crafts alkylation reactions were most facile when a strong electron donating group was located para to the aromatic carbon that attacks the conjugated enone system (e.g. **9b, 9d, 9e, 10b, 10d**, and **10e**). Substrates without this characteristic suffered from lower conversion. For example, electron releasing groups meta to the nucleophilic aromatic carbon (**9c** and **10c**) exerted a stronger inductive effect and the reaction suffered accordingly. Where regioisomeric ortho/para products could result (i.e. **9b, 9e, 10b**, and **10e**), complete selectivity for the para addition product was observed. Following chiral auxiliary removal, two-dimensional NMR experiments (see Supporting Information) confirmed both the structrure of the Friedel-Crafts products and the formation of the expected cis isomers.

L-Prolinol chiral auxiliary removal occurred efficiently through a previously reported procedure[33, 34] involving formation of an oxime and intramolecular isoxazolidinone formation (Table 5). Reduction of the N-O bond in **13**/**14** by $Mo(CO)_6$ facilitates hydrolysis and decarboxylation to provide **15**/**16**. Compound **12a** failed to undergo isoxazolidinone formation and therefore the chiral auxiliary could not be removed.

Palladium-catalyzed cycloalkenylation

A variety of approaches to form ring D and the bicyclo[3.2.1]octane with the palladium-catalyzed cycloalkenylation were explored. Initially, these included reactions with earlier structures, i.e. **10a, 10d, 12d**, and **14b**, where greater regiocontrol could be expected in the palladium-catalyzed cycloalkenylation. Consistent with literature reports on similar compounds[36–38], cyclohexenones **10a** and **10d** afforded a 75 and 66% yield of the cycloalkenylation product upon conversion to an enol silane and exposure to the standard cyclization conditions (10 mol% $Pd(OAc)_2$, O_2, DMSO, 45°C). However, both cycloalkenylation products failed to undergo the Friedel-Crafts alkylation. Attempted cycloalkenylation with **12d** was stymied by regioisomeric mixtures in the silylation step and with **14b**, by the absence of any enol silane formation.

With the failure of these approaches using earlier intermediates, attention turned to compounds **15** and **16** with the hope that a cycloalkenylation could be realized despite the rigidifying effect of the tricyclic structures and the regioselectivity challenges created by removal of the chiral auxiliary. A variety of silylation procedures were explored with **15d** and **16b**, the representative substrates chosen from the 6-5-6 and 6-6-6 tricyclic category, respectively. In both cases, standard enol silane formation conditions (TBS-OTf, Et_3N) afforded a 2:1 mixture of desired (**17** and **19**, Table 6) to undesired enol silane (**18** and **20**). Although trimethylsilyl (TMS) and triethylsilyl (TES) were also tried, tert-butyldimethylsilyl (TBS) enol ethers proved the most reproducible and stable for purification of the enol silane prior to the cycloalkenylation reaction. In addition, there is evidence from the Toyota lab that TBS enol silanes work best in palladium-catalyzed cycloalkenylation reactions[53]. The use of a bulkier base (iPr_2NEt), kinetic conditions (LiHMDS at −78°C) or a bromomagnesium diisopropylamide[54] failed to improve the yield or the ratio of desired to undesired enol silane. A small improvement in the regioisomeric

distribution was achieved by using a chiral lithium amide base[50, 55], which provided moderately better regioselectivity for **17** (2.5:1 versus **18**) from **15d** and even better results for the synthesis of **19** (4:1 versus **20**) from **16b**. Not unexpectedly, these silyl ether regioisomers could not be separated chromatographically; therefore they were subjected to the cycloalkenylation conditions as a mixture.

With the TBS enol silanes in hand, we were poised to attempt the palladium-catalyzed cycloalkenylation with the tricyclic substrates. For enol silane mixture **17**/**18**, treatment with $Pd(OAc)_2$ in DMSO under an oxygen atmosphere at 45°C resulted in selective cyclization of **17** to the desired tetracyclic structure **21** in a modest 41% yield (Table 7). The product was slightly contaminated by the undesired cycloalkenylation product **23** (5%) and unreacted enol silane **18** (6%). The use of different palladium catalysts ($Pd(OCOCF_3)_2$, $[Pd(CH_3CN)_4BF_4]$), or solvents (CH_3CN) failed to improve the outcome. A similar array of reaction conditions were also surveyed for cycloalkenylation of the enol silane mixture **19**/**20**. In the end, the best results were obtained with the slightly more electrophilic catalyst $Pd(OCOCF_3)_2$, however it afforded a mixture of four inseparable products: the two cycloalkenylation products, **25** and **27**, along with their alkene regioisomers, **26** and **28**. The overall yield of the four isomers was 60%, but the product was a 46:31:15:8 mixture of **25:26:27:28**. It should be noted that this distribution roughly parallels the 4:1 enol silane composition with **25** and **26** arising from **19**, and **27** and **28** derived from **20**. Running the reaction at a lower temperature (room temp.) failed to reduce the formation of alkene isomers. The richer mixture of products resulting from the 6-6-6 tricyclic system versus the 6-5-6 system is likely the result of slightly greater conformational flexibility which permits alternative reaction paths. In contrast, there was a greater proportion of the undesired silane **18** in the 6-5-6 tricycle, but very little of the corresponding cycloalkenylation products **23**/**24** actually formed. Nevertheless, the overall mixed results in the cycloalkenylation transformation of the 6-5-6 and 6-6-6 systems highlights the challenges of conducting the reaction on the more rigid tricyclic systems.

In an attempt to isomerize the alkene mixture **25–28** to the most thermodynamically stable regioisomers, presumably **26** and **28**, the mixture of **25–28** was exposed to pTsOH under benzene reflux conditions[56]. Unexpectedly and quite fortuitously, this resulted in complete conversion of the entire mixture to **26** in a 74% yield. We hypothesize that this rearrangement and isomerization occurs along the path shown in Figure 2. Protonation of the alkenes to form a tertiary carbocation and formation of the enol begins the process. Preliminary computational modeling suggests the empty tertiary carbocation p orbital is not far from the enol pi system. Consequently, a four-member transition state can permit 1,3-migration of the alkyl carbocation piece to the opposite alpha position generating the isomeric tertiary carbocation and enol. Elimination and isomerization affords the product **26**. Thermodynamic calculations support compound **26** as the most stable constitutional isomer among **25–28**. A similar attempt to isomerize the 6-5-6 tricyclic mixture of **21** and **23** noted above, failed to afford a similar transformation despite an analogous calculated thermodynamic preference for compound **22**.

Conclusion

An enantioselective procedure for the synthesis of the tetracarbocyclic skeleton of the gibberellins or the *ent*-kauranes has been illustrated. The reported results demonstrate another extension of the Birch-Cope sequence products, which in this case affords a diterpene natural product-like structure. An intramolecular Friedel-Crafts alkylation of the enone system demonstrates the ability of aromatic carbon nucleophiles to be used in conjugate addition reactions with the Birch-Cope sequence products. The tricarbocyclic products were subsequently subjected to palladium-catalyzed cycloalkenylation to create the challenging bicyclo[3.2.1]octane C/D ring system. The cycloalkenylation reaction was modestly successful and illustrated the challenges of conducting this reaction on more complex and rigid substrates. An unprecedented isomerization of the *ent*-kaurane skeleton under acid conditions provided a good yield of the final *ent*-kaurane-like structure from a mixture of alkene isomers. The overall process illustrates a new enantioselective procedure towards a complex and important natural product-like carbon skeleton.

Experimental

General Procedures

All reactants and reagents were commercially available and were used without further purification unless otherwise indicated. Anhydrous THF was obtained by distillation from benzophenone-sodium under nitrogen. All reactions were carried out under an inert atmosphere of argon or nitrogen unless otherwise indicated. Concentrated refers to the removal of solvent with a rotary evaporator at normal water aspirator pressure followed by further evacuation with a direct-drive rotary vane vacuum pump. Yields refer to chromatographically and spectroscopically pure (>95%) compounds, except as otherwise indicated. All new compounds were determined to be >95% pure by NMR and/or GC as indicated. Thin layer chromatography was performed using silica gel 60 Å precoated aluminum backed plates (0.25 mm thickness) with fluorescent indicator, which were cut. Developed TLC plates were visualized with UV light (254 nm), iodine, and *p*-anisaldehyde staining. Flash column chromatography was conducted with the indicated solvent system using normal phase silica gel 60 Å, 230–400 mesh. Optical rotation measurements were taken on a Perkin-Elmer 341 polarimeter.^{1}H and ^{13}C NMR spectra were recorded at 400 MHz. Chemical shifts are reported in δ values (ppm) relative to an internal reference (0.05% v/v) of tetramethylsilane (TMS) or residual $CHCl_3$ for ^{1}H NMR and $CDCl_3$in ^{13}C NMR. Peak splitting patterns in the ^{1}H NMR are reported as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR experiments were conducted with the attached proton test (APT) pulse sequence. ^{13}C multiplicities are reported as δ_u(up) for methyl and methine, and δ_d(down) for methylene and quaternary carbons. IR data was obtained with an FT-IR spectrometer. GC analyses were performed with an EI-MS detector fitted with a 30 m × 0.25 mm column filled with cross-linked 5% PH ME siloxane (0.25 μm film thickness); gas pressure 7.63 psi He. One method for analysis of samples involved heating from 70 to 250°C (10°C/min) and finally holding at 250°C for 7 min. HRMS were determined by electrospray ionization (ESI) using an infusion pump on a Thermo-Electron LTQ-FT 7T Fourier transform ion cyclotron resonance (FT-ICR) spectrometer. Samples

were dissolved in neat methanol and then diluted to a 90/10/0.01 solution of CH_3OH/H_2O/formic acid. Alternatively, for lower molecular weight samples, determinations were by solid probe desorption, chemical ionization (CI) at 35 eV, using methane as the ionizing gas, on a Micromasss (now Waters) AutoSpec-Ultima M high-resolution triple sector (EBE) mass spectrometer. Thermodynamic computational calculations were conducted with Spartan '14 v. 1.1.8 using density functional theory with EDF2 functional, basis set 6–31G* and toluene as the solvent.

General Procedures for Diarylmethylene Synthesis

Benzylboronic Pinacol Ester Coupling

Method A: Aryl iodide (1.0 eq.), $Pd_2(dba)_3$ (8 mol%), PPh_3 (1.0 eq.), Ag_2O (1.5 eq.) and benzylboronic acid pinacol ester (1.5 eq.) were dissolved in THF and heated overnight at 70°C. The next day the reaction mixture was passed through a plug of silica using EtOAc. The resulting solution was washed with five times with saturated sodium bicarbonate and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the diaryl methylene product. Pure product was obtained through column chromatography (EtOAc in heptanes)[47].

Method B: DMF (3 mL/mmol aryl halide) was added to a flask containing $Pd(OAc)_2$ (3 mol %) and SPhos (6 mol%). Next finely crushed K_3PO_4 (3.0 eq.) was added, followed by aryl halide (1.0 eq.) and boronic ester (2.0 eq.). This was heated to 60°C overnight. The next day the reaction mixture was diluted with EtOAc and this was washed two times with 20% NaOH, then brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure to yield the diaryl methylene product. Pure product was obtained through column chromatography (7:3 EtOAc in heptanes).[57]

Diarylmethylene 2a, Method A: Use of the general procedure with aryl iodide **1** (207.4 mg, 0.553 mmol) provided 130.2 mg of the diarylmethylene product, an 84% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.31-7.24 (m, 2H), 7.23-7.05 (m, 5H), 6.88-6.79 (m, 1H), 4.44-4.34 (m, 1H), 3.93 (s, 2H), 3.83-3.79 (2s, 3H), 3.78-3.70 (m, 1H), 3.60-3.51 (m, 1H), 3.41 (s, 2H), 3.27-3.14 (m, 1H), 3.00 (s, 2H), 2.07-1.98 (m, 1H), 1.97-1.86 (m, 2H), 1.82-1.69 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 130.5, 128.85, 128.80, 128.2, 126.1, 111.35, 111.28, 59.1, 58.7, 56.3, 55.8, 55.7; δ_d 168.0, 153.7, 141.2, 133.5, 127.7, 127.2, 73.4, 72.4, 48.4, 45.8, 40.9, 28.5, 27.8, 24.2, 22.2. GC t_R = 11.77 min. EI-MS *m/z* (%): 339 (M^+, 1), 307 (9), 294 (15), 225 (100). HRMS (CI) (m/z): [M+H]+ calcd for $C_{21}H_{26}NO_3$:340.1913, found: 340.1926.

Diarylmethylene 2b, Method A: Use of the general procedure with aryl iodide **1** (1.53 g, 4.08 mmol) provided 874 mg of the diarylmethylene product, a 58% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.24-7.6 (m, 3H), 6.88-6.69 (m, 4H), 4.42-4.38 (m, 1H), 3.91 (s, 2H), 3.84-3.80 (2s, 3H), 3.80-3.77 (2s, 3H), 3.77-3.72 (m, 1H), 3.60-3.52 (m, 1H), 3.42 (s, 2H), 3.29-3.17 (m, 1H), 3.01 (s, 2H), 2.07-1.98 (m, 1H), 1.97-1.87 (m, 2H), 1.82-1.72 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u130.51, 130.46, 129.4, 128.1, 121.2, 121.16, 114.6, 111.37, 111.33, 59.0, 58.5, 57.2, 56.3, 55.67, 55.61, 55.02, 55.00 ; δ_d 167.9, 159.7, 153.18, 153.6, 142.69, 142.56, 133.3, 127.5, 127.2, 73.4, 72.35,

48.4, 45.7, 40.8, 28.5, 27.6, 23.96, 22.2. GC t_R = 13.51 min. EI-MS *m/z* (%): 369 (M^+, 1), 337 (7), 324 (10), 255 (100). HRMS (CI) (m/z): [M+1]+ calcd for $C_{22}H_{28}NO_4$: 370.2018, found: 370.2022.

Diarylmethylene 2c, Method A: Use of the general procedure with aryl iodide **1**(531.0 mg, 1.42 mmol) provided 320.7 mg of the diarylmethylene product, a 61% yield based on GCMS. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.17-7.03 (m, 4H), 6.87-6.74 (m, 3H), 4.49-4.32, (m, 1H), 3.73 (s, 2H), 3.85-3.76 (m, 6H), 3.76-3.71 (m, 1H), 3.61-3.51 (m, 1H), 3.40 (s, 2H), 3.29-3.13 (m, 1H), 3.10-2.95 (m, 1H), 2.08-1.84 (m, 4H), 1.81-1.69 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 130.41, 130.38, 130.3, 130.2, 129.79, 129.75, 128.0, 127.7, 120.79, 120.73. 113.9, 111.3, 111.2, 111.15, 59.1, 58.7, 57.2, 56.3, 55.74, 55.67, 55.61, 55.2; δ_d 168.1, 157.97, 153.6, 133.99, 133.97, 133.26, 133.14, 127.5, 127.1, 73.4, 72.3, 48.4, 45.8, 40.0, 28.4, 28.9, 24.2, 22.2. GC t_R = 13.91 min. EI-MS *m/z* (%): 369 (M^+, 1), 337 (7), 324 (10), 255 (100). HRMS (CI) (m/z): [M+1]+ calcd for $C_{22}H_{28}NO_4$: 370.2018, found: 370.2018.

Diarylmethylene 2d, Method B: Use of the general procedure with aryl iodide **1** (191.6 mg, 0.511 mmol) provided 114.2 mg of the diarylmethylene product, a 56% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.19-7.02 (m, 2H), 6.88-6.74(m, 2H), 6.74-6.62 (m, 2H), 4.42-4.34 (m, 1H), 3.86 (s, 2H), 3.86-3.84 (2s, 3H), 3.82 (s, 3H), 3.81-3.78 (2s, 3H), 3.77-3.70 (m, 1H), 3.60-3.50 (m, 1H), 3.41 (s, 2H), 3.28-3.14 (m, 1H), 3.01 (s, 2H), 2.06-1.97 (m, 1H), 1.97-1.85 (m, 2H), 1.81-1.69 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 130.38, 130.35, 128.0, 120.87, 120.83, 112.17, 112.12, 111.27, 111.22, 59.1, 58.7, 57.2, 56.3, 55.9, 55.8, 55.7, 55.66; δ_d 168.1, 153.6, 148.9, 147.4, 133.78, 133.60, 127.5, 127.1, 73.4, 72.3, 48.4, 45.7, 40.4, 28.4, 28.77, 24.2, 22.2.GC t_R = 15.64 min. EI-MS *m/z* (%): 399 (M^+, 1), 367 (3), 354 (17), 285 (100). HRMS (CI) (m/z): [M+1]+ calcd for $C_{23}H_{30}NO_5$:400.2124, found: 400.2113.

Diarylmethylene 2e, Method A: Use of the general procedure with aryl iodide **1** (2.11 g, 5.62 mmol) provided 930 mg of the diarylmethylene product, a 47% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.22-7.06 (m, 3H), 7.05-6.92 (m, 3H), 6.89-6.78 (m, 1H), 4.50-4.35, (m, 1H), 3.89 (s, 2H), 3.85-3.79 (2s, 3H), 3.79-3.71 (m, 1H), 3.62-3.52 (m, 1H), 3.42 (s, 2H), 3.29-3.15 (m, 1H), 3.06-2.92 (m, 1H), 2.34-2.29 (2s, 3H), 2.08-1.86 (m, 4H), 1.83-1.70 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 130.52, 130.49, 129.66, 129.60, 128.3, 128.2, 126.8, 125.90, 125.84, 111.3, 59.1, 58.6, 57.2, 56.3, 55.76, 55.68, 21.4; δ_d 167.98, 153.7, 141.0, 140.96, 138.02, 133.6, 127.6, 127.2, 73.4, 72.4, 48.4, 45.8, 40.8, 28.5, 27.8, 24.8, 22.2. GC t_R = 12.28 min. EI-MS *m/z* (%): 353 (M^+, 1), 331 (7), 308 (10), 239 (10). HRMS (CI) (m/z): [M+1]+ calcd for $C_{22}H_{28}NO_3$: 354.2069, found: 354.2070.

General Procedures for the Heck Cross-Coupling Reaction

Method A, for electron-poor styrenes—A flame-dried flask was charged with $Pd(OAc)_2$ (0.15 eq.), K_2CO_3 (2.0 eq.), *N*,*N*-dimethyl-β-alanine (0.15 eq.), and styrene (1.5 eq.). Next aryl iodide (1.0 eq.) dissolved in NMP was added and this was heated to 130°C

overnight. The next day the reaction was concentrated directly onto silica under reduced pressure and purified via column chromatography (1:1 EtOAc in heptanes)[58].

Method B, for electron-rich styrenes—To a flask containing aryl iodide (1.0 eq.) was added triethylamine (1.5 eq.), $Pd(OAc)_2$ (0.10 eq.), and DMA. This was heated overnight at 120°C. The next day the reaction was concentrated directly onto silica under reduced pressure and purified via column chromatography (1:1 EtOAc in heptanes)[49].

Stilbene 3a, Method A: Use of the general procedure with aryl iodide **1** (2.81 g, 7.48 mmol) provided 2.02 g of the cross-coupled product in a 77% yield (as the desired product and a Heck regioisomer). ^{1}H NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ 7.54-7.42 (m, 3H), 7.41-7.31 (t, 2H, *J*=7.84 Hz), 7.31-7.22 (m, 2H), 7.12-6.97 (m, 2H), 6.96-6.86 (m, 1H), 4.50-4.39 (m, 1H), 3.87 (s, 3H), 3.83-3.73 (m, 1H), 3.67-3.54 (m, 1H), 3.45 (s, 2H), 3.34-3.19 (m, 1H), 3.16-3.07 (m, 1H), 2.10-1.88 (m, 4H), 1.85-1.73 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ_u 128.5, 128.47, 128.41, 128.0, 127.9, 127.3, 127.28, 127.25, 127.21, 126.1, 125.4, 111.3, 58.9, 58.6, 56.2, 55.6, 55.5, 29.3, 24.4; δ_d 177.1, 167.45, 167.41, 154.7, 137.2, 137.17, 130.1, 130.0, 127.8, 127.4, 73.4, 72.2, 49.1, 48.2, 45.7, 45.6, 30.4, 28.4, 28.0, 27.7, 24.0, 22.1, 17.4. GC t_R = 12.347 min. (Minor Heck regioisomer, 4.38%). EI-MS *m/z* (%): 351 (M^+, 2), 306 (11), 237 (100), 178 (11), 165 (11). t_R = 15.29 min (Major Heck regioisomer, 94.97%). EI-MS *m/z* (%): 351 (M^+, 6), 306 (11), 237 (100), 178 (14), 165 (15). HRMS (CI) (m/z): [M+1]+ calcd for $C_{22}H_{26}NO_3$: 352.1913, found: 352.1910.

Stilbene 3b, Method B: Use of the general procedure with aryl iodide **1** (4.79 g, 12.8 mmol) provided 4.88 g of the cross-coupled product in a 96% yield (as the desired product and a Heck regioisomer). ^{1}H NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ 7.52-7.43 (m, 2H), 7.31-7.25 (t, 2H, *J*=7.68 Hz), 7.12-7.06 (t, 1H, *J*=7.36 Hz), 7.05-6.98 (d, 2H, *J*=11.28 Hz), 6.96-6.86 (m, 1H), 6.84-6.80 (m, 1H), 4.50-4.40 (m, 1H), 3.89-3.83 (m, 6H), 3.83-3.53 (m, 2H), 3.48-3.40 (m, 2H), 3.33-3.20 (m, 1H), 3.15-3.06 (m, 1H), 2.10-1.88 (m, 4H), 1.86-1.73 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ_u 130.1, 130.02, 129.6, 129.2, 128.63, 128.60, 127.79, 127.7, 127.46, 127.4, 125.7, 120.86, 120.81, 120.79, 119.0, 113.9, 113.3, 113.13, 113.09, 111.58, 111.41, 111.18, 110.9, 59.1, 58.8, 57.3, 56.3, 56.2, 55.8, 55.75, 55.2; δ_d 167.74, 167.67, 159.46, 155.0, 154.89, 148.9, 138.8, 134.1, 130.36, 130.24, 128.2, 127.55, 113.64, 73.5, 72.34, 48.5, 45.8, 28.52, 28.47, 27.8, 24.2, 22.2, 20.3. GC t_R = 14.30 min. (Minor Heck regioisomer, 4.72%). EI-MS *m/z* (%): 381 (M^+, 1), 336 (8), 267 (100), 133 (8). t_R = 19.99 min. (Major Heck regioisomer, 92.79%). EI-MS *m/z* (%): 381 (M^+, 9), 336 (5), 267 (100), 133 (10). HRMS (CI) (m/z): [M +1]+ calcd for $C_{23}H_{28}NO_4$: 382.2018, found: 382.2007.

Stilbene 3c, Method B: Use of the general procedure with aryl iodide **1** (5.016 g, 13.4 mmol) provided 4.39 g of the cross-coupled product in an 86 % yield (as the desired product and a Heck regioisomer). ^{1}H NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ 7.42-7.35 (m, 3H), 7.29-7.19 (m, 1H), 6.96-6.78 (m, 5H), 4.46-4.37 (m, 1H), 3.83-3.76 (m, 6H), 3.76-3.70 (dd, 1H, 9.4 Hz) 3.61-3.47 (m, 1H), 3.40 (s, 2H), 3.31-3.15 (m, 1H), 3.14-3.01 (m, 1H), 2.05-1.82 (m, 4H), 1.81-1.66 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of

regioisomers and rotamers) δ_u 132.8, 132.29, 132.26, 132.74, 132.67, 130.19, 130.14, 129.4, 128.29, 128.25, 127.5, 127.06, 125.40, 125.33, 114.12, 114.04, 113.62, 113.57, 111.38, 59.1, 58.9, 56.3, 55.8, 55.3; δ_d 167.91, 167.83. 159.19, 154.5, 127.9, 73.5, 72.36, 72.25, 48.57, 48.58, 45.8, 28.5, 27.81, 27.78, 24.2, 22.2. GC t_R = 14.89 min. (Minor Heck regioisomer, 5.87%). EI-MS *m/z* (%): 381 (M^+, 1), 336 (10), 267 (100), 133 (8). t_R = 20.68 min. (Major Heck regioisomer, 92.92%). EI-MS *m/z* (%): 381 (M^+, 21), 336 (3), 267 (100), 133 (8). HRMS (CI) (m/z): [M+1]+ calcd for $C_{23}H_{28}NO_4$: 382.2018, found: 382.2031.

Stilbene 3d, Method B: Use of the general procedure with aryl iodide **1** (3.65 g, 9.73 mmol) provided 3.51 g of the cross-coupled product in an 88% yield (as the desired product and a Heck regioisomer). ^{1}H NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ 7.46-7.36 (m, 2H), 7.07-6.94 (m, 2H), 6.93-6.78 (m, 4H), 4.47-4.36 (m, 1H), 3.90 (s, 3H), 3.85 (s, 3H), 3.81 (m, 3H), 3.78-3.70 (m, 1H), 3.64-3.50 (m, 1H), 3.41 (s, 2H), 3.30-3.16 (m, 1H), 3.12-3.02 (m, 1H), 2.06-1.84 (m, 4H), 1.81-1.68 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ_u 130.05, 130.04, 128.25, 127.2, 125.6, 125.3, 120.9, 119.65, 119.61, 111.48, 111.39, 111.31, 110.88, 110.82, 108.7, 59.02, 59.01, 56.3, 55.86, 55.78, 55.70, 55. 64; δ_d 167.7, 154.5, 149.1, 148.6, 134.2, 130.52, 130.49, 130.44, 127.9, 127.46, 127.43, 112.3, 73.5, 72.3, 72.27, 48.3, 45.8, 28.5, 27.8, 24.1, 22.2. GC t_R = 16.66 min. (Minor Heck regioisomer, 8.57%). EI-MS *m/z* (%): 411 (M^+, 4), 366 (8), 297 (100), 148 (11). t_R = 25.84 min. (Major Heck regioisomer, 87.67%). EI-MS *m/z* (%): 411 (M^+, 13), 366 (1), 297 (100), 148 (13). HRMS (CI) (m/z): [M]+ calcd for $C_{24}H_{29}NO_5$: 411.2046, found: 411.2039.

Stilbene 3e, Method B: Use of the general procedure with aryl iodide **1** (3.13 g, 8.57 mmol) provided 2.78 g of the cross-coupled product in an 89% yield (as the desired product and a Heck regioisomer). ^{1}H NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ 7.47-7.41 (m, 2H), 7.33-7.18 (m, 3H), 7.17-6.82 (m, 4H), 4.49-4.36 (m, 1H), 3.82 (s, 3H), 3.79-3.72 (dd, 1H, 9.4 Hz) 3.65-3.47 (m, 1H), 3.43 (s, 2H), 3.31-3.16 (m, 1H), 3.17-3.02 (m, 1H), 2.36 (s, 3H), 2.13-1.84 (m, 4H), 1.81-1.68 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ_u 128.95, 128.93, 128.55, 128.52, 128.28, 128.24, 128.09, 127.60, 127.45, 127.28, 127.02, 125.56, 125.41, 125.36, 123.52, 111.4, 110.9, 59.1, 58.8, 57.4, 56.4, 55.8, 55.7, 21.4; δ_d 167.7, 154.97, 138.14, 138.12, 137.32, 137.27, 130.51, 130.4, 128.02, 113.28, 73.5, 72.40, 72.27, 48.5, 45.82, 45.76, 28.54, 27.8, 24.2, 22.2. GC t_R = 12.89 min. (Minor Heck regioisomer, 5.78%). EI-MS *m/z* (%): 365 (M^+, 1), 333 (10), 320 (14), 251 (100), 178 (14). t_R = 16.83 min. (Major Heck regioisomer, 94.21%). EI-MS *m/z* (%): 365 (M^+, 9), 333 (3), 320 (7), 251 (100), 178 (19). HRMS (CI) (m/z): [M+1]+ calcd for $C_{23}H_{28}NO_3$: 366.2069, found: 366.2072.

General Procedure for Alkene Hydrogenation: A flask containing alkene(1.0 eq.) was reduced under a hydrogen atmosphere in a Parr shaker hydrogenator with Pd/C (0.20 g/g alkene) and a 1:1 mixture of EtOAc and EtOH. After 4 h the reaction mixture was filtered through celite and concentrated under reduced pressure. The reduced product was then purified via column chromatography (1:1 EtOAc in heptanes).

Diaryl 4a: Use of the general procedure with alkene **3a** (2.32 g, 8.11 mmol) provided 2.09 g of the hydrogenated product in an 90% yield. ^{1}H NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ 7.30-7.21 (m, 2H), 7.22-6.99 (m, 5H), 6.83-6.78 (d, 1H, *J*=8.56 Hz), 4.44-4.35, (m, 1H), 3.85-3.77 (m, 3H), 3.77-3.70 (m, 1H), 3.60-3.50 (m, 1H), 3.41 (s, 2H), 3.25-3.10 (m, 1H), 3.09-2.95 (m, 1H), 2.87 (s, 4H), 2.07-1.84 (m, 4H),1.80-1.68 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ_u 130.06, 129.98, 128.47, 128.43, 128.30, 128. 25, 127.67, 125.89, 125.83, 111.2, 59.07, 58.71, 57.2, 56.2, 55.71, 55.62, 24.7; δ_d 177.3, 167.99. 153.5, 151.54, 151.45, 133.99, 133.90, 127.4, 127.03, 73.5, 72.4, 48.4, 45.7, 37.91, 37.88, 36.81, 36.72, 28.47, 28.17, 27.78, 24.2, 22.2. GC t_R = 11.98 min. (Minor Heck regioisomer, 4.66%). EI-MS *m/z* (%): 353 (M^+, 1), 321 (8), 308 (13), 239 (100), 164 (8). t_R = 12.57 min. (Major Heck regioisomer, 95.09%). EI-MS *m/z* (%): 353 (M^+, 1), 321 (7), 308 (11), 239 (100), 91 (8). HRMS (CI) (m/z): [M+1]+ calcd for $C_{22}H_{28}NO_3$: 354.2069, found: 354.2069.

Diaryl 4b: Use of the general procedure with alkene **3b** (4.67 g, 12.26 mmol) provided 3.91 g of the hydrogenated product in an 83% yield. ^{1}H NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ 7.24-7.16 (t, 1H, *J*=7.36 Hz), 7.16-7.11 (dd, 1H, *J*=8.40, 2.20 Hz), 7.07-7.03 (d, 1H, *J*=2.12 Hz), 6.87-6.80 (d, 1H, 8.44 Hz), 6.80-6.69 (m, 3H), 4.47-4.38, (m, 1H), 3.86-3.71 (m, 7H), 3.64-3.52 (m, 1H), 3.44 (s, 2H), 3.27-3.12 (m, 1H), 3.11-2.98 (m, 1H), 2.88 (s, 4H), 2.08-1.84 (m, 4H), 1.83-1.64 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ_u 130.07, 130.01, 129.29, 129.25, 127.7, 120.91, 120.85, 114.25, 114.19, 111.27, 111.22, 111.18, 111.04, 59.1, 58.7, 57.3, 56.2, 55.76, 55.65, 55.62, 55.1, 43.88, 43.82; δ_d 168.13, 168.06, 159.65, 159.60, 153.5, 143.2, 143.1, 134.0, 133.95, 127.06, 73.5, 72.4, 48.45, 48.41, 37.99, 37.95, 36.73, 36.62, 28.5, 27.8, 24.2, 22.2.GC t_R = 13.73 min. (Minor Heck regioisomer, 3.59%). EI-MS *m/z* (%): 383 (M^+, 1), 351 (5), 338 (8), 269 (100), 134 (7). t_R = 15.27 min. (Major Heck regioisomer, 95.30%). EI-MS *m/z* (%): 383 (M^+, 1), 351 (10), 338 (14), 269 (100), 134 (7). HRMS (CI) (m/z): [M+1]+ calcd for $C_{23}H_{30}NO_4$: 384.2175, found: 384.2191.

Diaryl 4c: Use of the general procedure with alkene **3c** (4.44 g, 11.7 mmol) provided 3.90 g of the hydrogenated product in an 87% yield. ^{1}H NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ 7.16-7.00 (m, 4H), 6.85-6.78 (m, 3H), 4.46-4.37 (m, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.76-3.73 (m, 1H), 3.59-3.51 (m, 1H), 3.42 (s, 2H), 3.24-3.11 (m, 1H), 3.10-2.98 (m, 1H), 2.83 (s, 4H), 2.06-1.98 (m, 2H), 1.98-1.86 (m, 2H), 1.80-1.70 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ_u 130.1, 130.0, 129.4, 129.36, 127.7, 113.74, 113.69, 111.15, 59.1, 58.8, 57.3, 56.26, 56.21, 55.74, 55.63, 55.23;δ_d 168.1, 157.8, 134.1, 134.0, 133.7 133.6, 127.4, 73.5, 72.4, 48.4, 45.8, 37.12, 37.04, 37.03, 28.5, 27.8, 24.2, 22.26, 22.22.GC t_R = 13.99 min. (Minor Heck regioisomer, 10.20%). EI-MS *m/z* (%): 383 (M^+, not shown due to loss of two methyl groups in the GC-MS), 351 (7), 338 (10), 269 (100), 126 (10). t_R = 14.76 min. (Major Heck regioisomer, 89.49%). EI-MS *m/z* (%): 383 (M^+, 1), 351 (7), 338 (12), 269 (100), 121 (15). HRMS (CI) (m/z): [M+1]+ calcd for $C_{23}H_{30}NO_4$: 384.2175, found: 384.2162.

Diaryl 4d: Use of the general procedure with alkene **3d** (3.51 g, 8.54 mmol) provided 3.12 g of the hydrogenated product in an 88% yield. ^{1}H NMR ($CDCl_3$, a mixture of regioisomers

and rotamers) δ 7.13-7.03 (td, 2H, *J*=8.08, 2.48 Hz), 6.83-6.74 (m, 2H), 6.72-6.63 (m, 2H), 4.45-4.36, (m, 1H), 3.85 (s, 4H), 2.83 (s, 2H), 3.82-3.78 (m, 3H), 3.77-3.70 (m, 1H), 3.61-3.5 (m, 1H), 3.41 (s, 2H), 3.27-3.11 (m, 1H), 3.10-2.96 (m, 1H), 2.83 (s, 4H), 2.06-1.85 (m, 4H), 1.82-1.67 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ_u 130.12, 130.6, 127.7, 120.31, 120.28, 111.94, 111.87, 111.25, 111.23, 111.16, 59.1, 59.7, 58.6, 57.3, 56.26, 56.22, 55.89, 55.83, 55.80, 55.79, 55.78, 55.74, 55.63, 43.4; δ_d 168.1, 148.8, 147.33, 147.26, 134.23, 134.14, 134.05, 133.96, 127.5, 127.07, 73.5, 72.4, 48.4, 45.7, 37.5, 37.0, 36.95, 28.45, 27.8, 24.2, 22.2. GC t_R = 15.59 min. (Minor Heck regioisomer, 5.82%). EI-MS *m/z* (%): 413 (M^+, 2), 381 (3), 368 (7), 299 (100), 149 (8). t_R = 16.86 min. (Major Heck regioisomer, 91.76%). EI-MS *m/z* (%): 413 (M^+, 5), 381 (3), 368 (8), 299 (100), 151 (18). HRMS (CI) (m/z): [M+1]+ calcd for $C_{23}H_{32}NO_5$: 414.2280, found: 414.2279.

Diaryl 4e: Use of the general procedure with alkene **3e** (3.10 g, 8.49 mmol) provided 3.12 g of the hydrogenated product in an 85% yield. ^{1}H NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ 7.19-7.05 (m, 2H), 7.01-6.87 (m, 4H), 6.84-6.73 (d, 1H, *J*=7.2 Hz), 4.46-4.32 (m, 1H), 3.80-3.64 (m, 4H), 3.60-3.47 (m, 1H), 3.41-3.35 (s, 2H), 3.22-2.93 (m, 2H), 2.88-2.76 (s, 4H), 2.32-2.26 (s, 3H), 2.05-1.80 (m, 2H). ^{13}C NMR ($CDCl_3$, a mixture of regioisomers and rotamers) δ_u 130.07, 130.00, 129.30, 129.26, 128.25, 127.7, 126.7, 126.6, 125.50, 125.46, 111.2, 59.1, 58.7, 57.30, 56.2, 55.78, 55.67, 43.8, 21.4; δ_d 168.2, 153.6, 141.5, 141.48, 137.90, 137.88, 134.27, 134.13, 73.55, 72.45, 48.4, 45.8, 37.91, 36.90, 36.81, 28.5, 27.8, 22.2. GC t_R = 12.42 min. (Minor Heck regioisomer, 5.74%). EI-MS *m/z* (%): 367 (M^+, 1), 335 (10), 322 (13), 253 (100). t_R = 13.14 min. (Major Heck regioisomer, 93.26%). EI-MS *m/z* (%): 367 (M^+, 2), 335 (8), 322 (10), 253 (100), 105 (24). HRMS (CI) (m/z): [M +1]+ calcd for $C_{23}H_{30}NO_3$: 368.2226, found:368.2215.

General Procedure for Birch Reduction-Allylation: To a solution of benzamide (1.0 eq.) and tert-butyl alcohol (1.0 eq.) in THF (10 mL/mmol amide) and NH_3 (130 mL/mmol amide) at −78°C was added potassium in small pieces until blue coloration was maintained for 20 min. Isoprene was added dropwise to consume the excess metal, and then allyl bromide (2.5 eq.) was added. The solution was stirred at −78°C and allowed to slowly warm to room temperature to allow the NH_3 to evaporate. Water was then added, and the mixture was extracted three times with DCM. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to yield the 2,5-cyclohexadiene product. Pure product was obtained through column chromatography (3:7 EtOAc in heptanes). Note: Birch reduction-allylation products were not stable enough to obtain an HRMS or optical rotations.

Cyclohexadiene 5a: Use of the general procedure with benzamide **2a** (1.1710 g, 3.45 mmol) provided 0.640 g of the 2,5-cyclohexadiene product in a 49% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.28 (t, 2H, *J*=7.80 Hz), 7.22-7.12 (m, 3H), 5.73-5.55 (m, 1H), 5.25 (s, 1H), 5.07-4.90 (m, 2H), 4.68 (t, 1H, *J*=3.44 Hz), 4.39-4.26 (m, 1H), 3.67-3.55 (m, 1H), 3.47 (s, 3H), 3.38-3.25 (m, 6H), 3.23-3.11 (m, 1H), 2.87-2.47 (m, 3H), 1.91-1.74 (m, 3H), 1.74-1.59 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 135.1, 128.8,

128.3, 126.3, 122.8, 92.6, 58.9, 58.1, 54.2; δ_d 170.7, 152.5, 139.3, 136.9, 116.8, 72.1, 52.8, 46.0, 43.3, 41.3, 29.3, 26.6, 24.8.

Cyclohexadiene 5b: Use of the general procedure with benzamide **2b** (0.971 g, 2.63 mmol) provided 0.497 g of the 2,5-cyclohexadiene product in a 46% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.18 (t, 1H, *J*=7.72 Hz), 6.79-6.65 (m, 3H), 5.70-5.56 (m, 1H), 5.24 (s, 1H), 5.04-4.89 (m, 2H), 4.68 (t, 1H, *J*=3.64 Hz), 4.36-4.24 (m, 1H), 3.78 (s, 3H), 3.68-3.56 (m, 1H), 3.49 (t, 2H, *J*=2.12 Hz), 3.46 (s, 2H), 3.37-3.26 (m, 6H), 2.91-2.28 (m, 3H), 1.93-1.76 (m, 3H), 1.74-1.54 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 135.1, 129.3, 122.9, 121.2, 114.7, 111.4, 92.6, 58.9, 58.1, 55.1, 54.23; δ_d 170.7, 159.7, 153.0, 140.9, 136.8, 116.8, 72.0, 52.8, 46.1, 43.3, 41.1, 29.4, 26.5, 24.9.

Cyclohexadiene 5c: Use of the general procedure with benzamide **2c** (1.07 g, 2.89 mmol) provided 0.8359 g of the 2,5-cyclohexadiene product in a 70% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.13-7.00 (t, 2H, *J*=7.24 Hz), 6.87-6.76 (d, 2H, *J*=8.60 Hz), 5.70-5.54 (m, 1H), 5.24-5.17 (d, 1H, *J*=7.32 Hz), 5.03-4.89 (m, 2H), 4.67 (s, 1H), 4.38-4.26, (m, 1H), 3.78 (s, 3H), 3.66-3.50 (m, 2H), 3.46 (s, 3H), 3.39-3.30 (m, 4H), 3.30-3.12 (m, 3H), 2.89-2.44 (m, 4H), 1.93-1.73 (m, 3H), 1.74-1.59 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 135.2, 129.7, 123.1, 122.4, 113.74, 113.71, 92.76, 92.65, 58.92, 58.88, 58.04, 57.89, 55.23, 54.25, 54.21; δ_d 170.8, 170.3, 158.2, 152.9, 152.5, 137.3, 136.9, 131.4, 131.3, 116.7, 72.17, 72.07, 52.8, 52.77, 46.2, 46.0, 42.3, 41.28, 41.27, 29.31, 29.26, 26.6, 26.4, 25.0, 24.8, 22.7.

Cyclohexadiene 5d: Use of the general procedure with benzamide **2d** (2.62 g, 6.34 mmol) provided 2.07 g of the 2,5-cyclohexadiene product in a 72% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 6.78-6.71 (d, 1H, *J*=8.0 Hz), 6.71-6.59 (m, 2H), 5.67-5.53 (m, 1H), 5.19 (s, 1H), 5.00-4.84 (m, 2H), 4.64 (s, 1H), 4.33-4.21, (m, 1H), 3.84-3.75 (m, 7H), 3.61-3.46 (m, 2H), 3.43 (s, 3H), 3.37-3.10 (m, 6H), 2.84-2.68 (m, 1H), 2.68-2.60 (m, 1H), 2.60-2.43 (m, 2H), 1.91-1.70 (m, 3H), 1.69-1.54 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 135.2, 123.2, 122.5, 120.9, 112.0, 111.1, 92.7, 58.9, 58.1, 57.9, 55.9, 55.8, 54.3, 54.2; δ_d 170.3, 152.9, 148.9, 147.5, 137.1, 136.9, 131.9, 116.1, 72.6, 72.02, 72.0, 51.3, 47.7, 46.3, 46.0, 43.0, 41.3, 29.7, 29.3, 29.3, 26.9, 26.5, 26.4, 25.2, 25.0, 24.9.

Cyclohexadiene 5e: Use of the general procedure with benzamide **2e** (0.880 g, 2.49 mmol) provided 0.60 g of the 2,5-cyclohexadiene product in a 61% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.17 (t, 1H, *J*=7.48 Hz), 7.08-6.91 (m, 3H), 5.73-5.53 (m, 1H), 5.27 (s, 1H), 5.09-4.88 (m, 2H), 4.68 (t, 1H, *J*=3.52 Hz), 4.41-4.27, (m, 1H), 3.70-3.60 (m, 1H), 3.60-3.52 (m, 1H), 3.48 (s, 3H), 3.41-3.24 (m, 6H), 3.23-3.14 (m, 1H), 2.87-2.52 (m, 4H), 2.33 (2s, 3H), 1.75-1.57 (m, 2H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 135.5, 129.7, 129.66, 128.2, 127.0, 125.9, 123.3, 92.7, 59.0, 57.9, 54.3, 21.4; δ_d 170.8, 170.3, 152.9, 152.5, 139.2, 137.9, 136.9, 116.7, 72.1, 52.8, 46.1, 43.2, 41.3, 29.4, 26.6.

Cyclohexadiene 6a: Use of the general procedure with benzamide **4a** (3.45 g, 9.77 mmol) as 2 separate Birch reductions which were combined for purification provided 3.74 g of the 2,5-cyclohexadiene product in a 97% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.31-7.22 (t, 2H, *J*=5.28 Hz), 7.22-7.13 (d, 3H, *J*=6.52 Hz), 5.60-5.45 (m, 1H), 5.15 (s, 1H),

4.99-4.85, (m, 2H), 4.73-4.68 (t, 1H, 3.56 Hz), 4.31-4.24 (m, 1H), 3.62-3.57 (dd, 1H, J=9.6, 3.2 Hz), 3.47 (s, 3H), 3.33 (s, 3H), 3.31-3.15 (m, 3H), 2.89-2.63 (m, 5H), 2.53- 2.45 (m, 1H), 2.43-2.35 (t, 2H, J=8.00 Hz), 1.87-1.56 (m, 5H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 135.0, 128.3, 128.2, 125.9, 121.6, 92.7, 58.8, 58.1, 54.2;δ_d170.3, 152.99, 141.45, 136.6, 116.5, 71.9, 52.6, 45.8, 45.3, 37.5, 33.9, 29.9, 26.3, 24.9.

Cyclohexadiene 6b: Use of the general procedure with benzamide **4b** (8.52 g, 22.2 mmol) as 3 separate Birch reductions which were combined for purification to provide 6.96 g of the 2,5-cyclohexadiene product in a 73% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.24-7.17 (m, 1H), 6.83-6.70 (m, 3H), 5.63-5.47 (m, 1H), 5.17 (s, 1H), 5.00-4.88 (m, 2H), 4.73 (t, 1H, *J*=3.64 Hz), 4.36-4.24 (m, 1H), 3.81 (s, 3H), 3.66-3.59 (m, 1H), 3.50 (s, 3H), 3.39-3.33 (m, 3H), 3.33-3.17 (m, 2H), 3.89-2.65 (m, 5H), 2.56-2.46 (m, 1H), 2.40 (t, 2H, *J*=8.04 Hz), 1.90-1.70 (m, 3H), 1.68-1.59 (m, 2H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 135.1, 129.3, 121.6, 120.7, 114.1, 111.1, 92.6, 58.9, 58.1, 55.1, 54.2; δ_d 170.5, 159.7, 153.0, 143.1, 136.6, 116.6, 71.9, 45.9, 41.3, 37.4, 34.1, 29.9, 26.3, 24.8.

Cyclohexadiene 6c: Use of the general procedure with benzamide **4c** (0.500 g, 1.30 mmol) provided 0.290 g of the 2,5-cyclohexadiene product in a 52% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.14-7.04 (d, 2H, *J*=8.52 Hz), 6.85-6.76 (d, 2H, *J*=10.7 Hz) 5.66-5.44 (m, 1H), 5.13 (s, 1H), 5.00-4.85 (m, 2H), 4.74-4.67 (t, 1H, *J*=3.56 Hz), 4.36-4.22 (m, 1H), 3.75 (s, 3H), 3.66-3.54 (m, 1H), 3.47 (s, 3H), 3.33 (s, 3H), 3.30-3.13 (m, 3H), 2.91-2.61 (m, 4H), 2.56-2.41 (m, 1H), 2.40-2.31 (t, 2H, *J*=3.96 Hz), 2.02-1.53 (m, 5H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 135.1, 129.24, 129.14, 128.23, 128.18, 121.5, 113.73, 113.69, 113.62, 92.6, 58.9, 58.0, 55.2, 54.2 ;δ_d 170.8, 157.8, 136.7, 133.5, 116.54, 72.0, 52.6, 45.9, 41.29, 41.06, 37.7, 33.1, 29.9, 26.3, 24.9.

Cyclohexadiene 6d: Use of the general procedure with benzamide **4d** (2.62 g, 6.34 mmol) provided 2.07 g of the 2,5-cyclohexadiene product in a 72% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 6.80-6.67 (m, 3H), 5.64-5.46 (m, 1H), 5.19-5.12 (d, 1H, *J*=9.56 Hz), 4.98-4.87 (m, 2H), 4.74-4.69 (t, 1H, *J*=3.92 Hz), 4.36-4.23 (m, 1H), 3.89-3.86 (d, 3H, *J*= 2.44 Hz), 3.86-3.82 (d, 3H, *J*=2.28 Hz), 3.65-3.52 (m, 1H), 3.49 (s, 3H), 3.37-3.31 (d, 3H, *J*=4.00 Hz), 3.32-3.16 (m, 3H), 2.60-2.29 (m, 3H), 2.90-2.62 (m, 4H), 1.89-1.57 (m, 5H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 134.33, 134.30, 126.22, 126.19, 112.2, 110.61, 110.68, 55.4, 44.2, 38.4;δ_d171.3, 164.2, 159.1, 159.07, 142.0, 136.4, 118.1, 118.06, 102.7, 45.7, 42.9, 41.1, 27.7, 18.9.

Cyclohexadiene 6e: Use of the general procedure with benzamide **4e** (1.6299 g, 4.44 mmol) provided 1.43 g of the 2,5-cyclohexadiene product in a 78% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.14 (t, 1H, *J*=7.36 Hz), 7.02-6.91 (m, 3H), 5.66-5.46 (m, 1H), 5.15 (s, 1H), 5.00-4.86 (m, 2H), 4.71 (t, 1H, *J*=3.48 Hz), 4.35-4.21 (m, 1H), 3.61-3.57 (m, 1H), 3.33 (s, 3H), 3.27-3.13 (m, 1H), 2.90-2.62 (m, 4H), 2.56-2.44 (m, 1H), 2.35 (t, 2H, *J*=3.96 Hz), 2.31 (2, 3H), 1.88-1.53 (m, 4H), 1.42-1.30 (m, 1H).^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 135.1, 129.0, 128.2, 126.6, 125.2, 121.5, 92.6, 58.8, 58.1, 54.2, 21.4; δ_d 170.3, 153.0, 141.4, 137.8, 136.7, 116.5, 71.97, 52.6, 45.9, 41.3, 37.6, 34.1, 29.9, 26.3, 24.8.

General Procedure for Enol Ether Hydrolysis: Enol ether (1.0 eq.) was dissolved in MeOH (6 mL/mmol enol ether), cooled to 0°C, and treated with 6 N HCl (2.5 mL/mmol enol ether). After stirring overnight, the reaction solution was diluted with water and extracted three times with DCM. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Column chromatography (1:1 EtOAc in heptanes) afforded pure ketone.

Ketone 7a: Use of the general procedure with enol ether **5a** (0.64 g, 1.68 mmol) provided 0.5411 g of the ketone product in an 88% yield. $[\alpha]_D^{24} = -16.5$ (c=0.4, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.33-7.26 (m, 2H), 7.26-7.20 (m, 1H), 7.19-7.23 (m, 2H), 5.90-5.73 (m, 1H), 5.49 (s, 1H), 5.09-4.99 (m, 2H), 4.34-4.21 (m, 1H), 3.66-3.59 (m, 1H), 3.42 (s, 2H), 3.39 (s, 3H), 3.33 (m, 1H), 3.28-3.12 (m, 1H), 3.07-2.96 (m, 1H), 2.73-2.65 (d, 2H, *J*=7.36 Hz), 2.60-2.29 (m, 4H), 1.96-1.76 (m, 3H), 1.76-1.61 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u134.3, 134.2, 128.73, 128.70, 128.55, 126.6, 124.9, 124.4, 59.0, 57.9; δ_d 208.2, 207.7, 169.0, 168.5, 139.3, 138.6, 118.2, 72.1, 71.9, 61.2, 46.7, 46.4, 43.7, 41.9, 41.6, 37.0, 36.9, 28.4, 28.2, 26.8, 26.7, 24.6. HRMS (CI) (m/z): [M+1]+ calcd for $C_{23}H_{30}NO_3$: 368.2226, found: 368.2235.

Ketone 7b: Use of the general procedure with enol ether **5b** (0.497 g, 1.21 mmol) provided 0.362 g of the ketone product in a 75% yield. $[\alpha]_D^{24} = -14.8$ (c=0.73, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.25-7.17 (t, 1H, *J*=7.80 Hz), 6.81-6.67 (m, 3H), 5.89-5.74 (m, 1H), 5.48 (s, 1H), 5.10-4.98 (m, 2H), 4.34-4.21 (m, 1H), 3.78 (m, 2H), 3.67-3.58 (m, 1H), 3.43-3.29 (m, 6H), 3.30-3.18 (m, 1H), 3.10-2.96 (m, 1H), 2.72-2.64 (d, 2H, *J*=7.32 Hz), 2.62-2.26 (m, 4H), 1.93-1.79 (m, 4H), 1.80-1.58 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 134.3, 129.5, 124.5, 121.1, 114.8, 111.6, 59.0, 57.9, 55.1; δ_d 168.5, 159.7, 140.2, 139.1, 118.2, 118.19, 71.8, 61.2, 46.5, 46.4, 43.7, 41.6, 37.3, 36.9, 28.2, 26.9, 24.5. HRMS (CI) (m/z): [M+1]+ calcd for $C_{24}H_{32}NO_4$: 398.2331, found: 398.2333.

Ketone 7c: Use of the general procedure with enol ether **5c** (0.8359 g, 2.24 mmol) provided 0.7329 g of the ketone product in a 91% yield. ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.07-6.95 (dd, 2H, *J*=8.64, 2.36 Hz), 6.80-6.75 (d, 2H, *J*=8.52), 5.87-5.68 (m, 1H), 5.41-4.34 (d, 1H, *J*=8.04 Hz), 5.05-4.92 (m, 2H), 4.30-4.15 (m, 1H), 3.73 (s, 3H), 3.6-3.40 (m, 1H), 3.39-3.28 (m, 6H), 3.25-3.08 (m, 1H), 3.04-2.88 (m, 1H), 2.70-2.55 (d, 2H), 2.55-2.22 (m, 4H), 1.91-1.73 (m, 3H), 1.73-1.56 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 134.3, 134.25, 129.7, 129.66, 124.5, 124.1, 114.0, 113.9, 59.02, 59.0, 57.8, 55.3; δ_d 208.3, 207.8, 169.0, 168.5, 158.4, 139.6, 139.2, 130.63, 130.60, 118.15, 118.13, 72.1, 71.9, 61.3, 61.2, 46.8, 46.4, 42.9, 41.9, 41.6, 37.0, 36.9, 28.4, 28.2, 26.8, 26.7, 24.6. A sample of compound **7c** decomposed before an HRMS or optical rotation could be obtained.

Ketone 7d: Use of the general procedure with enol ether **5d** (0.990 g, 2.24 mmol) provided 0.959 g of the ketone product in an 85% yield. $[\alpha]_D^{24} = -20.6$ (c=0.47, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 6.74-6.69 (d, 1H, *J*=7.84 Hz), 6.67-6.60 (m, 2H), 5.83-5.70 (m, 1H), 5.40 (s, 1H), 5.04-4.92 (m, 2H), 4.28-4.14 (m, 1H), 3.80 (s, 6H), 3.61-3.39 (m, 1H), 3.38-3.08 (m, 7H), 3.05-2.93 (m, 1H), 2.65-2.55 (d, 2H, *J*=7.72 Hz), 2.53-2.42 (m, 1H), 2.42-2.25 (m, 3H), 1.92-1.72 (m, 3H), 1.72-1.55 (m, 1H). ^{13}C NMR

($CDCl_3$, a mixture of rotamers) δ_u 134.3, 134.2, 124.6, 124.2, 119.3, 112.0, 111.3, 58.95, 57.9; δ_d 208.2, 207.8, 168.5, 149.0, 147.8, 138.5, 139.1, 131.16, 131.13, 118.1, 72.2, 71.8, 61.3, 61.2, 55.9, 55.8, 46.8, 46.5, 43.2, 41.7, 41.4, 37.0, 36.9, 28.3, 28.2, 26.8, 26.7, 24.7, 24.6. HRMS (CI) (m/z): [M+1]+ calcd for $C_{25}H_{34}NO_5$: 428.2437, found: 428.2448.

Ketone 7e: Use of the general procedure with enol ether **5e** (0.60 g, 1.52 mmol) provided 0.360 g of the ketone product in a 62% yield. $[\alpha]_D^{24}$ = −14.2 (c=0.33, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.19 (t, 1H, *J*=7.44 Hz), 7.08-7.03 (d, 1H, *J*=7.56), 7.01-6.92 (m, 2H), 5.92-5.76 (m, 1H), 5.48 (s, 1H), 5.11-4.99 (m, 2H), 4.39-4.19 (m, 1H), 3.69-3.47 (m, 1H), 3.43-3.30 (m, 6H), 3.30-3.18 (m, 1H), 3.08-2.93 (m, 1H), 2.74-2.64 (d, 2H, *J*=7.36 Hz), 2.59-2.35 (m, 4H), 2.34 (s, 3H), 1.95-1.78 (m, 3H), 1.77-1.60 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 134.3, 134.27, 129.5, 128.4, 127.3, 125.7, 124.7, 124.3, 59.00, 58.98, 57.9, 21.4; δ_d 208.3, 169.0, 168.5, 139.3, 138.6, 137.9, 118.0, 72.1, 71.9, 61.2, 46.8, 46.4, 43.4, 41.9, 41.7, 37.0, 36.7, 28.4, 28.2, 26.83, 26.81, 24.9. HRMS (CI) (m/z): [M+1]+ calcd for $C_{24}H_{32}NO_3$: 382.2382, found: 382.2391.

Ketone 8a: Use of the general procedure with enol ether **6a** (1.69 g, 4.28 mmol) provided 1.48 g of the ketone product in a 91 % yield. $[\alpha]_D^{24}$ = −7.8 (c=0.27, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.35-7.25 (m, 2H), 7.24-7.12 (m, 3H), 5.82-5.62 (m, 1H), 5.37 (s, 1H), 5.11-4.93 (m, 2H), 4.35-4.17 (m, 1H), 3.65-3.56 (dd, 1H, *J*=9.32 Hz, *J*=3.04 Hz), 3.34 (s, 3H), 3.33-3.26 (m, 1H), 3.10-2.99 (m, 1H), 2.97-2.85 (m, 1H), 2.83-2.74 (t, 2H, *J*=6.52 Hz), 2.65-2.53 (m, 3H), 2.51-2.38 (m, 5H), 1.92-1.71 (m, 3H), 1.70-1.56 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u134.3, 128.3, 128.2, 126.0, 123.3, 58.8, 57.8; δ_d207.5, 168.4, 141.0, 139.1, 117.8, 71.7, 60.95, 46.3, 41.3, 38.2, 36.7, 22.6, 28.3, 26.5, 24.4. HRMS (CI) (m/z): [M+1]+ calcd for $C_{24}H_{32}NO_3$: 382.2382, found: 382.2377.

Ketone 8b: Use of the general procedure with enol ether **6b** (2.52 g, 5.93mmol) provided 1.72 g of the ketone product in a 72% yield.$[\alpha]_D^{24}$= −7.6 (c=0.67, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.26-7.17 (t, 1H, *J*=7.80 Hz), 6.82-6.70 (m, 3H), 5.82-5.64 (m, 1H), 5.37 (s, 1H), 5.12-4.95 (m, 2H), 4.35-4.17 (m, 1H), 3.80 (s, 3H), 3.62 (dd, 1H, *J*=9.32, 3.20 Hz), 3.36 (s, 3H), 3.34-3.26 (m, 1H), 3.12-3.01 (m, 1H), 2.97-2.88 (m, 1H), 2.83-2.74 (t, 2H, *J*=8.00 Hz), 2.65-2.53 (m, 3H), 2.52-2.39 (m, 5H), 1.98-1.73 (m, 3H), 1.71-1.57 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u134.3, 129.4, 123.3, 120.6, 114.2, 111.1, 58.9, 57.8, 55.1; δ_d207.9, 168.4, 159.7, 142.6, 138.9, 118.1, 71.9, 61.0, 46.6, 41.7. 38.1, 36.9, 33.7, 28.4, 26.6, 24.5. HRMS (CI) (m/z): [M+1]+ calcd for $C_{25}H_{34}NO_4$: 412.2488, found: 412.2474.

Ketone 8c: Use of the general procedure with enol ether **6c** (1.40 g, 3.29 mmol) provided 0.880 g of the ketone product in a 65% yield. $[\alpha]_D^{24}$ = −12.8 (c=0.53, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.07-6.95 (d, 2H, *J*=8.48 Hz), 6.79-6.70 (d, 2H, *J*=8.48 Hz), 5.82-5.56 (m, 1H), 5.26 (s, 1H), 5.04-4.86 (m, 2H), 4.26-4.09 (m, 1H), 3.75-3.36 (m, 3H), 3.58-3.50 (dd, 1H, *J*=9.24, 3.20 Hz), 3.27 (s, 3H), 3.26-3.19 (m, 2H), 3.00-2.90 (m, 1H), 2.85-2.75 (m, 1H), 2.71-2.61 (m, 2H), 2.56-2.44 (m, 3H), 2.43-2.31 (m, 5H), 1.88-1.62 (m, 3H), 1.61-1.49 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u134.3, 129.2, 123.4, 113.8, 113.8, 59.03, 58.98, 55.26, 55.23; δ_d 168.5, 157.9, 139.1, 133.0, 128.2, 128.12,

118.0, 71.99, 71.7, 61.16, 61.1, 46.3, 41.6, 41.5, 38.5, 36.9, 32.9, 28.5, 26.6, 24.6, 24.5. HRMS (CI) (m/z): [M+1]+ calcd for $C_{25}H_{33}NO_4$: 412.2488, found: 412.2471.

Ketone 8d: Use of the general procedure with enol ether **6d** (1.82 g, 4.00 mmol) provided 1.58 g of the ketone product in a 90% yield. $[\alpha]_D^{24} = -17.7$ (c=0.6, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 6.82-6.75 (d, 1H, *J*=7.92 Hz), 6.72 (s, 1H), 6.69 (s, 1H), 5.84-5.67 (m, 1H), 5.41-5.34 (d, 1H, *J*=5.00 Hz), 5.11-4.94 (m, 2H), 4.34-4.16 (m, 1H), 3.86 (s, 3H), 3.85-3.83 (d, 3H, *J*=1.28 Hz), 3.63-3.41 (m, 1H), 3.34 (s, 2H), 3.31 (s, 2H), 3.14-2.98 (m, 1H), 2.97-2.87 (m, 1H), 2.79-2.66 (t, 2H, *J*=7.68 Hz), 2.65-2.53 (m, 3H), 2.52-2.38 (m, 5H), 1.93-1.72 (m, 3H), 1.71-1.59 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 155.1, 132.8, 128.5, 128.2, 126.1, 59.1, 58.9, 57.9, 56.4; δ_d 195.51, 195.53, 165.5, 142.6, 142.3, 137.81, 137.76, 119.4, 74.0, 72.1, 48.3, 46.1, 41.9, 41.6, 39.8, 39.75, 38.7, 34.0, 33.9, 30.8, 30.7, 30.5, 30.4, 28.5, 27.7, 24.3, 22.1. HRMS (CI) (m/z): [M+1]+ calcd for $C_{26}H_{36}NO_5$: 442.2593, found: 442.2576.

Ketone 8e: Use of the general procedure with enol ether **6e** (1.43 g, 3.50 mmol) provided 1.30 g of the ketone product in a 94% yield. $[\alpha]_D^{24} = -6.1$ (c=0.67, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.18 (t, 1H, *J*=7.48 Hz), 7.05-6.94 (m, 3H), 5.86-5.64 (m, 1H), 5.38 (s, 1H), 5.13-4.94 (m, 2H), 4.34-4.17 (m, 1H), 3.69-3.42 (m, 1H), 3.36 (s, 3H), 3.34-3.26 (m, 1H), 3.14-3.03 (m, 1H), 2.98-2.87 (m, 1H), 2.76 (t, 2H, *J*=7.80 Hz), 2.66-2.51 (m, 3H), 2.51-2.41 (m, 5H), 2.33 (s, 3H), 1.95-1.74 (m, 3H), 1.73-1.56 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 134.4, 129.0, 128.2, 126.7, 125.2, 123.2, 58.8, 57.8, 21.3; δ_d 207.5, 207.46, 168.9, 168.4, 168.35, 140.9, 139.2, 137.8, 117.8, 71.95, 71.7, 60.97, 46.5, 46.3, 41.6, 41.4, 38.2, 36.7, 33.7, 28.5, 28.4, 26.7, 26.6, 24.5. HRMS (CI) (m/z): [M+1]+ calcd for $C_{25}H_{34}NO_3$: 396.2539, found: 396.2534.

General Procedure for the Cope Rearrangement: The 1,5-diene (1.0 eq.) was dissolved in 1,2-dichlorobenzene (2 mL/mmol diene) and refluxed overnight. The solvent was removed in vacuo and the crude enone was purified by chromatography (EtOAc).

Enone 9a: Use of the general procedure with 1,5-diene **7a** (0.541 g, 1.47 mmol) provided 0.320 g of the pure enone product in a 59% yield. $[\alpha]_D^{24} = -44.2$ (c=1.0, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.35-7.21 (m, 3H), 7.21-7.12 (m, 2H), 6.82 (s, 1H), 5.94-5.78 (m, 1H), 5.25-5.11 (m, 2H), 4.34-4.25 (m, 1H), 3.73-3.61 (m, 1H), 3.51-3.40 (m, 1H), 3.37 (s, 2H), 3.22 (s, 1H), 3.15-3.03 (m, 1H), 3.03-2.91 (m, 1H), 2.90-2.79 (d, 2H, *J*=10.4 Hz), 2.57-2.21 (m, 4H), 2.04-1.79 (m, 5H), 1.79-1.68 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 155.09, 155.0 133.2, 133.0, 130.4, 128.4, 128.3, 126.9, 126.8, 59.1, 58.9, 57.8, 56.4; δ_d 195.0, 165.9, 165.8, 138.5, 136.5, 119.6, 119.5, 74.1, 72.2, 48.3, 45.7, 44.4, 44.3, 43.9, 42.9, 42.8, 41.3, 39.9, 34.1, 34.0, 30.5, 30.3, 30.2, 28.5, 27.7, 24.3, 24.2, 22.0.GC t_R = 13.15 min. EI-MS *m/z* (%): 367 (M^+, 6), 322 (99), 276 (16), 253 (39), 91 (100). HRMS (CI) (m/z): [M+1]+ calcd for $C_{23}H_{30}NO_3$: 368.2226, found: 368.2218.

Enone 9b: Use of the general procedure with 1,5-diene **7b** (0.4004 g, 1.01 mmol) provided 0.235 g of the pure enone product in a 59% yield. $[\alpha]_D^{24} = -31.3$ (c=0.53, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.23-7.15 (t, 1H, *J*=8.00 Hz), 6.84-6.70 (M, 3H), 6.68 (s, 1H), 5.93-5.76 (m, 1H), 5.22-5.11 (t, 2H, *J*=9.96 Hz), 4.33-4.23 (m, 1H), 3.80-3.75

(d, 3H, *J*=4.00 Hz), 3.67-3.62 (dd, 1H, *J*=9.44, 3.40 Hz), 3.48-3.40 (m, 1H), 3.36 (s, 2H), 3.20 (s, 1H), 3.14-3.07 (m, 1H), 3.05-2.96 (m, 1H), 2.81 (s, 1H), 2.53-2.23 (m, 4H), 2.03-1.81 (m, 6H), 1.79-1.68 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 155.0, 133.2, 133.0, 129.3, 129.2, 122.8, 122.78, 119.6, 119.5, 116.4, 112.0, 111.9, 59.1, 58.9, 57.8, 56.4, 55.2, 55.19; δ_d 195.1, 165.8, 159.5, 138.5, 138.2, 138.0, 119.6, 119.5, 74.1, 72.2, 48.3, 45.7, 44.5, 43.9, 43.0, 42.4, 39.9, 39.7, 34.1, 34.0, 30.5, 30.3, 29.7, 28.5, 27.7, 24.2, 22.0.GC t_R = 15.31 min. (Major isomer, 94.45%). EI-MS *m/z* (%): 397 (M^+, 5), 352 (73), 283 (20), 121 (100). HRMS (CI) (m/z): [M+1]+ calcd for $C_{24}H_{32}NO_4$: 398.2331, found: 398.2332.

Enone 9c: Use of the general procedure with 1,5-diene **7c** (0.7329 g, 1.85 mmol) provided 0.5869 g of the pure enone product, a mixture of rotamers in an 80% yield. $[\alpha]_D^{24}$ = −60.8 (c=0.13, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.08-6.96 (m, 2H), 6.82-6.69 (m, 3H), 5.85-5.70 (m, 1H), 5.16-5.02 (m, 2H), 4.26-4.17 (m, 1H), 3.71 (s, 3H), 3.64-3.55 (m, 1H), 3.43-3.33 (m, 1H), 3.33-3.28 (m, 2H), 3.17-3.13 (m, 1H), 3.10-3.29 (m, 2H), 2.78-2.67 (m, 2H), 2.46-2.30 (m, 2H), 2.30-2.13 (m, 2H), 1.94-1.77 (m, 5H), 1.74-1.61 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 134.3, 134.2, 133.25, 133.17, 133.14, 131.4, 131.37, 131.3, 129.7, 113.96, 113.94, 113.81, 113.76, 113.72, 113.68, 59.11, 58.90, 58.55, 57.84, 57.74, 57.56, 56.37, 56.34, 55.26, 55.22; δ_d 195.6, 195.5, 195.1, 195.7, 166.3, 165.92, 165.86, 165.83, 158.5, 158.3, 155.3, 155.2, 154.7, 138.5, 138.0, 137.9, 128.55, 128.43, 128.38, 128.30, 119.45, 119.41, 119.38, 118.1, 74.04, 74.03, 72.21, 72.16, 72.11, 48.33, 48.30, 46.75, 46.43, 45.66, 45.48, 43.5, 43.4, 42.99, 42.90, 42.85, 42.80, 42.3, 39.95, 39.90, 39.82, 37.02, 36.92, 34.10, 34.04, 34.01, 33.98, 30.5, 3.4, 30.24, 30.18, 28.5, 28.3, 27.7, 24.2, 24.2, 21.99, 21.95. GC t_R = 16.01 min. EI-MS *m/z* (%): 397 (M^+, 3), 352 (6), 121 (100). HRMS (CI) (m/z): [M +1]+ calcd for $C_{24}H_{32}NO_4$: 398.2331, found: 398.2343.

Enone 9d: Use of the general procedure with 1,5-diene **7d** (0.8188 g, 1.92 mmol) provided 0.6026 g of the pure enone product in a 73% yield. $[\alpha]_D^{24}$ = −22.2 (c=0.33, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 6.83-6.75 (m, 2H), 6.75-6.70 (m, 1H), 6.70-6.66 (m, 1H), 5.92-5.76 (m, 1H), 5.23-5.10 (m, 2H), 4.33-4.23 (m, 1H), 3.89-3.84 (m, 6H), 3.67-3.59 (dd, 1H, *J*=9.36, 3.32 Hz), 3.48-3.41 (m, 1H), 3.36 (s, 2H), 3.22 (s, 1H), 3.17-3.09 (m, 1H), 3.09-3.00 (m, 1H), 2.88-2.72 (m, 1H), 2.53-2.37 (m, 2H), 2.37-2.21 (m, 2H), 2.07-1.84 (m, 5H), 1.79-1.67 (m, 1H).^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 133.25,133.2, 133.1122.5, 122.5, 113.75, 113.70, 113.6, 111.08, 111.01, 110.98, 59.1, 58.9, 57.9, 57.5, 56.34, 56.32, 56.01, 55.99, 55.87; δ_d 195.5, 195.4, 195.08, 195.98, 165.9, 165.8, 155.3, 155.2, 154.3, 148.7, 148.0, 138.4, 137.8, 129.0, 128.98, 128.81, 119.5, 119.4, 74.1, 72.3, 72.2, 53.4, 48.33, 48.26, 45.7, 45.5, 44.03, 43.6, 43.5, 43.0, 42.5, 39.9, 39.8, 39.77, 39.69, 34.1, 33.98, 30.8, 30.6, 30.5, 28.6, 28.3, 27.7, 27.6, 24.2, 24.1, 22.0, 21.9. GC t_R = 18.69 min. EI-MS *m/z* (%): 427 (M^+, 4), 382 (4), 151 (100). HRMS (CI) (m/z): [M]+ calcd for $C_{25}H_{34}NO_5$: 428.2437, found: 428.2420.

Enone 9e: Use of the general procedure with 1,5-diene **7e** (0.360 g, 0.945 mmol) provided 0.25 g of the pure enone product in a 69% yield. $[\alpha]_D^{24}$ = −22.8 (c=1.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.23-7.13 (m, 1H), 7.10-7.02 (m, 1H), 7.01-6.93 (m, 2H), 6.81 (s, 1H), 5.95-5.78 (m, 1H), 5.25-5.10 (m, 2H), 4.35-4.24 (m, 1H), 3.71-3.60 (m, 1H),

3.50-3.40 (m, 1H), 3.40 (s, 2H), 3.20 (s, 1H), 3.17-2.93 (m, 2H), 2.87-2.76 (m, 2H), 2.54-2.36 (m, 2H), 2.37-2.25 (m, 5H), 2.20-1.83 (m, 5H), 1.81-1.67 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 134.27, 134.21, 134.03, 129.5, 128.8, 127.6, 125.0, 124.4, 121.1, 114.8, 111.6, 59.0, 57.97, 57.88, 55.1; δ_d 168.5, 159.8, 140.2, 139.1, 118.24, 118.20, 77.0, 71.8, 61.6, 61.2, 46.5, 46.4, 43.7, 41.6, 41.5, 37.2, 36.9, 28.4, 28.2, 26.7, 25.9, 24.5. GC t_R = 18.69 min. EI-MS *m/z* (%): 381 (M^+, 3), 336 (46), 267 (14), 105 (100). HRMS (CI) (m/z): [M+1]+ calcd for $C_{24}H_{32}NO_3$: 382.2382, found: 382.2374.

Enone 10a: Use of the general procedure with 1,5-diene **8a** (2.60 g, 6.82 mmol) provided 1.96 g of the pure enone product in a 75% yield. $[\alpha]_D^{24}$ = −31.8 (c=0.67, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.34-7.24 (m, 2H), 7.23-7.12 (m, 3H), 6.89-6.83 (m, 1H), 5.91-5.75 (m, 1H), 5.24-5.13 (m, 2H), 4.36-4.26 (m, 1H), 3.71-3.62 (m, 1H), 3.51-3.43 (m, 1H), 3.38 (s, 2H), 3.30-3.22 (m, 1H), 3.21-3.12 (m, 2H), 2.75-2.59 (m, 2H), 2.57-2.51 (t, 2H, *J*=6.96 Hz), 2.42-2.34 (t, 2H, *J*=7.80 Hz), 2.06-1.87 (m, 5H), 1.87-1.75 (m, 3H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u155.1, 154.7132.9, 132.8, 128.5, 128.2, 128.1, 126.1, 59.1, 58.9, 57.9, 56.4; δ_d 195.5, 194.0, 166.0, 165.6, 141.6, 138.2, 137.8, 119.3, 74.0, 72.0, 48.3, 45.5, 42.0, 41.7, 39.8, 39.7, 38.7, 33.97, 33.93, 39.77, 30.69, 30.44, 30.38, 28.5, 27.6, 24.2, 22.0. GC t_R = 14.98 min. (Major isomer, 93.62%). EI-MS *m/z* (%): 381 (M^+, 3), 336 (56), 267 (60), 135 (34), 91 (100). t_R = 15.18 min (Minor isomer, 6.12%). EI-MS *m/z* (%): 381 (M^+, 5), 336 (82), 267 (61), 91 (100). HRMS (CI) (m/z): [M+1]+ calcd for $C_{24}H_{32}NO_3$: 382.2382, found: 382.2386.

Enone 10b: Use of the general procedure with 1,5-diene **8b** (1.72 g, 4.20 mmol) provided 1.32 g of the pure enone product in a 76% yield. $[\alpha]_D^{24}$ = −30.3 (c=0.73, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.34-7.24 (m, 2H), 7.08-6.98 (t, 1H, *J*=8.40 Hz), 6.69 (s, 1H), 6.65-6.50 (m, 3H), 5.74-5.59 (m, 1H), 5.09-4.96 (m, 2H), 4.18-4.08 (m, 1H), 3.60 (s, 3H), 3.54-3.45 (dd, 1H, *J*=9.32, 3.20 Hz), 3.35-3.25 (t, 1H, *J*=8.04 Hz), 3.20 (s, 2H), 3.15-2.98 (m, 3H), 2.53-2.41 (m, 2H), 2.41-2.31 (t, 2H, *J*=6.48 Hz), 2.26-2.14 (t, 2H, *J*=7.28 Hz), 1.88-1.70 (m, 5H), 1.70-1.57 (m, 3H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 155.151.1, 154.4, 132.8, 132.77, 129.5, 120.54, 120.49, 114.1, 111.2, 111.18, 59.06, 58.94, 57.9, 56.4, 55.1,14.2; δ_d 195.6, 195.1, 166.0, 165.8, 159.7, 143.2, 143.2, 138.2, 137.8, 137.7, 119.4, 74.2, 72.1, 48.5, 45.5, 41.9, 41.6, 39.61, 39.4, 38.6, 33.93, 33.90, 30.72, 30.64, 30.46, 30.40, 28.5, 27.6, 24.2, 22.0. GC t_R = 18.02 min. (Major isomer, 92.69%). EI-MS *m/z* (%): 411 (M^+, 10), 366 (100), 297 (53), 135 (48), 121 (94). t_R = 18.51 min (Minor isomer, 6.77%). EI-MS *m/z* (%): 411 (M^+, 10), 366 (73), 297 (100), 121 (55). HRMS (CI) (m/z): [M +1]+ calcd for $C_{25}H_{34}NO_4$: 412.2488, found: 412.2482.

Enone 10c: Use of the general procedure with 1,5-diene **8c** (1.00 g, 2.43 mmol) provided 0.630 g of the pure enone product in a 63% yield. $[\alpha]_D^{24}$ = −22.1 (c=1.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.14-7.05 (d, 2H, *J*=8.56 Hz), 6.91-6.81 (t, 3H, *J*=8.56 Hz), 5.93-5.76 (m, 1H), 5.25-5.11 (m, 2H), 4.37-4.27 (m, 1H), 3.80 (s, 4H), 3.73-3.63 (dd, 1H, *J*=9.48, 3.32 Hz), 3.54-3.43 (m, 1H), 3.39 (s, 2H), 3.31-3.23 (m, 1H), 3.19 (m, 2H), 3.69-3.51 (m, 4H), 2.43-2.35 (m, 2H), 2.05-1.88 (m, 6H), 1.86-1.73 (m, 1H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 155.38, 154.8, 132.9, 132.8, 129.1, 129.05, 114.0, 59.1, 59.0, 57.9, 56.4, 55.3; δ_d 195.65, 195.15, 166.0, 165.9, 158.0, 138.14, 137.7, 133.7, 74.2,

72.2, 48.4, 45.5, 41.9, 41.6, 40.0, 38.7, 34.0, 33.95, 30.79, 30.71, 29.54, 29.49, 28.5, 27.8, 24.3. GC t_R = 18.69 min. (Major isomer, 94.45%). EI-MS *m/z* (%): 411 (M^+, 3), 366 (22), 297 (22), 277 (15), 121 (100). t_R = 19.06 min. (Minor isomer, 5.49%). 411 (M^+, 4), 366 (36), 297 (17), 121 (100). HRMS (CI) (m/z): [M+1]+ calcd for $C_{25}H_{34}NO_4$: 412.2488, found: 412.2476.

Enone 10d: Use of the general procedure with 1,5-diene **8d** (1.58 g, 3.58 mmol) provided 1.14 g of the pure enone product in a 72% yield. $[\alpha]_D^{24}$ = −33.2 (c=1.7, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 6.89-6.85 (d, 1H, *J*=2.24 Hz), 6.83-6.77 (d, 1H, *J*=8.04 Hz), 6.74-6.66 (dd, 2H, *J*=10.08, 1.92 Hz), 5.92-5.76 (m, 1H), 5.25-5.13 (m, 2H), 4.36-4.25 (m, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.71-3.61 (m, 1H), 3.51-3.41 (m, 1H), 3.37 (s, 2H), 3.30-3.15 (m, 3H), 2.67-2.58 (m, 2H), 2.57-2.51 (t, 2H, *J*=7.32 Hz), 2.42-2.34 (t, 2H, *J*=7.48 Hz), 2.06-1.81 (m, 5H), 1.87-1.75 (m, 3H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 155.1, 132.8, 120.0, 111.6, 111.4, 59.0, 58.9, 57.85, 57.73, 56.3, 55.87, 55.82, 14.1; δ_d 295.5, 195.0, 166.0, 165.3, 148.9, 147.4, 138.1, 137.78, 137.65, 134.2, 119.2, 74.2, 72.14, 72.09, 60.24, 48.4, 48.39, 45.5, 45.4, 42.1, 42., 41.9, 41.6, 39.8, 39.7, 38.6, 33.93, 33.89, 30.8, 30.7, 29.97, 28.4, 27.6, 24.2, 21.95. GC t_R = 21.85 min. (Major isomer, 95.49%). EI-MS *m/z* (%): 441 (M^+, 3), 396 (17), 327 (22), 277 (13), 151 (100). t_R = 22.58 min. (Minor isomer, 4.5%). EI-MS *m/z* (%): 441 (M^+, 8), 396 (40), 327 (45), 277 (36), 151 (100). HRMS (CI) (m/z): [M+1]+ calcd for $C_{26}H_{36}NO_5$: 442.2593, found:442.2572.

Enone 10e: Use of the general procedure with 1,5-diene **8e** (1.30 g, 3.29 mmol) provided 1.10 g of the pure enone product in a 84% yield. $[\alpha]_D^{24}$ = −27.5 (c=0.4, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.14 (t, 1H, *J*=7.44 Hz), 7.04-6.89 (m, 3H), 6.85 (s, 1H), 5.90-5.72 (m, 1H), 5.22-5.09 (m, 2H), 4.34-4.22 (m, 1H), 3.70-3.60 (m, 1H), 3.50-3.40 (m, 1H), 3.36 (s, 2H), 3.29-3.11 (m, 3H), 2.55-2.55 (m, 2H), 2.52 (t, 2H, *J*=6.83 Hz), 2.40-2.32 (m, 2H), 2.30 (s, 3H), 2.00-1.84 (m, 5H), 1.85-1.70 (m, 3H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 155.2, 154.7, 132.9, 132.8, 129.0, 129.97, 128.4, 126.8, 125.2, 125.18, 59.1, 58.9, 57.8, 56.4, 21.3, 14.2; δ_d 195.5, 195.2, 166.0, 165.9, 141.6, 138.2, 138.1, 137.8, 119.3, 74.2, 72.2, 60.3, 48.3, 46.4, 46.3, 41.9, 41.7, 39.8, 38.7, 34.0, 33.9, 30.77, 30.67, 30.38, 30.33, 28.5, 27.6, 24.2, 22.0. GC t_R = 15.66 min. (Major isomer, 93.34%). EI-MS *m/z* (%): 395 (M^+, 6), 350 (77), 281 (43), 105 (100). t_R = 16.00 min. (Minor isomer, 5.13%). 395 (M^+, 10), 350 (100), 281 (78), 105 (77). HRMS (CI) (m/z): [M+1]+ calcd for $C_{25}H_{34}NO_3$: 396.2539, found: 396.2536.

General Procedure for Friedel-Crafts Conjugate Addition: Under an argon atmosphere, enone (1.0 eq.) was dissolved in DCM (8 mL/mmol enone). The mixture was cooled to 0°C and $BF_3{\cdot}Et_2O$ (1.2 eq.) was added dropwise. The reaction was then left to warm to room temperature and stirred overnight. The next day the reaction was quenched with saturated NH_4Cl and water. The aqueous layer was extracted 3× with DCM and the combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified using column chromatography (1:1 EtOAc in heptanes).

Tricyclic Compound 11b: Use of the general procedure with enone **9b** (92.3 mg, 0.232 mmol) provided 90.5 mg of the tricyclic product in as a mixture of inseparable epimers in a 98% yield. $[\alpha]_D^{24}$ = −201 (c=0.17, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers and epimers) δ 7.13-6.94 (m, 1H), 6.80-6.70 (m, 1H), 6.70-6.59 (m, 1H), 5.98-5.73 (m, 1H), 5.22-4.96 (m, 2H), 4.77-4.30 (m, 1H), 4.00 (s, 1H), 3.96-3.87 (m, 1H), 3.77 (s, 3H), 3.74-3.67 (m, 1H), 3.60-3.51 (dd, 1H, *J*=9.84, 2.44 Hz), 3.50-3.42 (m, 2H), 3.42-3.33 (m, 1H), 3.33-3.25 (m, 1H), 3.06-2.79 (m, 2H), 2.66-2.37 (m, 3H), 2.37-2.20 (m, 2H), 2.21-1.80 (m, 5H), 1.72-1.44 (m, 2H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers and epimers) δ_u 134.3, 134.2, 134.1, 124.6, 124.4, 123.7, 112.3, 112.2, 111.15, 111.96, 111.89, 111.70, 111.64, 111.18, 110.2, 61.6, 59.3, 59.18, 59.4, 57.4, 55.4, 47.2, 46.7; δ_d 178.0, 177.2, 166.7, 159.23, 159.18, 142.9, 142.5, 138.0, 137.97, 118.37, 118.20, 118.15, 117.98, 96.4, 74.8, 73.7, 72.4, 71.7, 50.3, 49.6, 48.8, 47.0, 43.9, 43.3, 4.4, 4.3, 36.5, 29.7, 29.2, 28.8, 28.6, 26.4, 25.8, 25.3, 25.0, 19.8. HRMS (ESI) (m/z): [M+1]+ calcd for $C_{24}H_{32}NO_4$: 398.2326, found: 398.2323.

Tricyclic Compound 11d: Use of the general procedure with enone **9d** (233.7 mg, 0.548 mmol) provided 227.6 mg of the tricyclic product in as a mixture of epimers in a 97% yield. $[\alpha]_D^{24}$ = +8.6 (c=0.27, CH_2Cl_2). Less polar epimer: ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 6.80-6.74 (d, 1H, *J*=7.76 Hz), 6.58 (s, 0.65H), 6.39 (s, 0.14H), 6.32 (s, 0.14H), 5.96-5.81 (m, 1H), 5.22-5.09 (m, 2H), 4.81-4.71 (m, 1H), 4.12-3.96 (m, 2H), 3.96-3.89 (m, 1H), 4.12-3.96 (m, 1H), 3.96-3.89 (m, 1H), 3.85 (s, 1H), 3.82 (s, 2H), 3.75-3.62 (m, 1H), 3.58-3.50 (dd, 1H, *J*=10.0, 3.16 Hz), 3.42-3.30 (m, 3H), 3.05-2.91 (m, 1H), 2.61-2.39 (m, 3H), 2.36-2.23 (m, 2H), 2.03-1.89 (m, 4H), 1.70-1.44 (m, 3H). More polar epimer: (fractions 9–35) ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 6.74 (s, 0.5H), 6.73 (d, 1H, *J*=5.12 Hz), 6.67 (s, 0.5H), 5.88-5.73 (m, 1H), 5.15-5.00 (m, 2H), 4.51-4.28 (m, 1H), 3.90-3.82 (m, 3H), 3.81-3.75 (m, 3H), 3.51-3.13 (m, 4H), 3.09-2.71 (m, 4H), 2.66-2.57 (m, 1H), 2.55-2.36 (m, 2H), 2.33-2.20 (m, 2H), 2.19-2.12 (m, 1H), 2.06-1.87 (m, 4H), 1.88-1.68 (m, 2H). Less polar epimer: ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u134.5, 134.4, 109.3, 109.2, 109.0, 108.3, 107.7, 107.3, 61.7, 61.6, 59.26, 59.21, 59.18, 57.4, 56.43, 56.39, 56.13, 56.11, 47.4, 47.3, 21.0, 14.2, 14.1; δ_d 178.6, 178.3, 177.8, 166.7, 148.72, 148.62, 148.49, 148.32, 138.0, 137.8, 137.5, 133.3, 133.2, 132.9, 118.14, 118.08, 117.96, 95.8, 73.6, 73.0, 72.4, 60.3, 50.3, 49.6, 49.0, 47.7, 47.3, 47.2, 43.6, 43.2, 40.4, 40.3, 39.9, 31.9, 29.7, 29.4, 28.9, 28.8, 26.7, 26.1, 25.9, 25.3, 25.1, 22.7, 20.0. More polar epimer: ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 134.2, 134.1, 134.05, 108.7, 108.3, 108.0, 107.73, 107.71, 107.57, 107.33, 59.1, 58.9, 58.7, 58.4, 57.8, 57.7, 57.3, 57.2, 57.0, 56.6, 56.4, 56., 55.9, 53.1, 52.0, 51.75, 51.71, 31.6, 14.1; δ_d 209.1, 208.5, 208.2, 168.4, 167.9, 148.8, 148.7, 148.2, 148.1, 136.4, 136.3, 136.0, 135.8, 132.9, 132.8, 118.4, 118.3, 114.0, 75.1, 74.9, 72.7, 71.7, 47.3, 47.2, 46.3, 45.9, 45.0, 44.8, 44.66, 44.61, 44.0, 43.89, 43.85, 43.73, 43.68, 36.5, 36.4, 33.8, 31.9, 31.2, 31.01, 30.97, 30.89, 29.7, 29.5, 29.3, 29.2, 29.1, 28.9, 27.5, 27.4, 24.0, 23.8, 22.7, 22.3. HRMS (ESI) (m/z): [M+1]+ calcd for $C_{25}H_{34}NO_5$: 428.2432, found: 428.2428.

Tricyclic Compound 11e: Use of the general procedure with enone **9e** (211.8 mg, 0.534 mmol) provided 189.2 mg of an inseparable mixture of 2 epimers, a 76% yield. $[\alpha]_D^{24}$ = −154 (c=0.53, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers and epimers) δ 7.09-6.86 (m, 3H), 6.03-5.81 (m, 1H), 5.24-5.07 (m, 2H), 4.81-4.49 (m, 1H), 4.05 (s, 1H), 3.98-3.87 (m, 1H), 3.81-3.65 (m, 1H), 3.62-3.53 (m, 1H), 3.47 (s, 2H), 3.35-3.26 (m, 1H), 3.06-2.90

(m, 1H), 2.66-2.41 (m, 3H), 2.49-2.22 (m, 5H), 2.21-1.82 (m, 5H), 1.76-1.45 (m, 3H). ^{13}C NMR ($CDCl_3$) δ_u134.5, 134.4, 127.6, 127.5, 126.3, 126.0, 123.7, 122.9, 61.7, 59.3, 59.0, 47.1, 21.2; δ_d178.3, 143.0, 141.0, 136.8, 118.1, 73.7, 72.4, 49.6, 46.8, 43.1, 40.4, 29.2, 28.6, 26.5, 25.8, 25.3, 24.9. HRMS (ESI) (m/z): [M+1]+ calcd for $C_{24}H_{32}NO_3$: 382.2377, found: 382.2374.

Tricyclic Compound 12a: Use of the general procedure with enone **10a** (71.5 mg, 0.188 mmol) provided 45.1 mg of the pure tricyclic product in a 63% yield (as a mixture of epimers and rotomers). $[\alpha]_D^{24}$ = −78.3 (c=0.33, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.34-7.25 (m, 2H), 7.25-7.11 (m, 2H), 6.03-5.75 (m, 1H), 5.24-5.10 (m, 2H), 4.76-4.65, 4.49-4.31 (m, 1H), 3.78-3.49 (m, 2H), 3.45-3.25 (m, 2H), 3.12-2.96 (m, 1H), 2.86-2.30 (m, 4H), 2.30-2.14 (m, 2H), 2.14-1.91 (m, 5H), 1.91-1.76 (m, 1H), 1.74-1.51 (m, 3H), 1.48-1.36 (m, 3H). ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 134.3, 133.9, 128.5, 128.4, 126.5, 125.6, 84.2, 62.4, 61.6, 60.8, 59.1, 58.3, 41.1; δ_d 208.9, 172.9, 142.7, 118.6, 118.1, 73.6, 72.2, 71.9, 64.0, 49.2, 44.9, 42.2, 42.0, 36.7, 35.6, 35.5, 34.2, 33.8, 30.5, 30.3, 27.1, 27.0, 26.8, 26.3, 25.4, 25.1. HRMS (ESI) (m/z): [M+1]+ calcd for $C_{24}H_{32}NO_3$: 382.2377, found: 382.2372.

Tricyclic Compound 12b: Use of the general procedure with enone **10b** (750 mg, 1.82 mmol) provided 662.2 mg of the pure tricyclic product as a 1:1 mixture of two epimers in an 88% yield. $[\alpha]_D^{24}$ = −128 (c=0.2, CH_2Cl_2). Less polar epimer: ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 6.88-6.79 (d, 1H, *J*=9.24 Hz), 6.76-6.62 (m, 2H), 6.03-5.85 (m, 1H), 5.24-5.05 (m, 2H), 4.77-4.61 (m, 1H), 3.99-3.82 (m, 1H), 3.78 (s, 3H), 3.74-3.59 (m, 2H), 3.59-3.48 (m, 1H), 3.48-3.40 (m, 1H), 3.38 (s, 2H), 3.35-3.27 (m, 1H), 2.82-2.62 (m, 2H), 2.58-2.39 (m, 1H), 2.39-2.16 (m, 3H), 2.11-1.52 (m, 6H), 1.50-1.32 (m, 3H). More polar epimer: ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.13-6.95 (dd, 1H, *J*=37.6, 8.52 Hz), 6.67-6.61 (dd, 1H, *J*=9.48, 2.72 Hz), 6.60-6.64 (dd, 1H, J=8.48, 2.72 Hz), 5.89-5.74 (m, 1H), 5.11-4.91 (m, 2H), 4.25-4.15 (m, 1H), 3.74 (s, 3H), 3.70-3.49 (m, 2H), 3.42-3.27 (m, 3H), 3.19-3.02 (m, 1H), 2.96-2.87 (m, 3H), 2.52-2.37 (m, 2H), 2.28-2.10 (m, 2H), 2.00-1.80 (m, 5H), 1.80-1.70 (m, 2H), 1.65-1.54 (m, 2H), 1.54-1.41 (m, 1H). Less polar epimer: ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 134.3, 134.16, 134.07, 133.89, 128.5, 128.4, 127.9, 127.7, 124.04, 113.5, 113.4, 111.3, 113.2, 113.1, 111.7, 111.6, 111.5, 111.4, 111.2, 61.7, 61.6, 61.5, 59.2, 59.1, .5, 55.4, 55.2, 41.3, 41.5, 37.0; δ_d 178.59, 178.57, 177.9, 166.6, 158.46, 158.29, 158.17, 146.8, 139.7, 138.6, 138.3, 138.5, 131.73, 131.66, 118.7, 118.5, 118.3, 118.1, 97.0, 95.8, 74.0, 73.8, 72.4, 72.34, 72.27, 72.18, 50.3, 48.9, 48.8, 42.1, 41.9, 37.2, 36.8, 36.6, 36.4, 35.8, 34.4, 34.3, 34.1, 33.9, 29.7, 29.3, 29.0, 28.8, 28.4, 28.0, 27.54, 27.48, 27.32, 27.14, 26.6, 26.5, 26.3, 24.7, 25.4, 24.2, 25.05, 24.9, 22.7, 21.8, 19.5. More polar epimer: ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 133.7, 133.6, 131.4, 130.9, 113.7, 113.6, 111.6, 111.5, 61.3, 60.9, 60.8, 60.4, 59.2, 59.0, 58.7, 57.0, 56.6, 56.3, 55.2, 55.17, 48.0, 46.9, 46.7, 46.5; δ_d 207.1, 206.6, 168.4, 158.3, 135.6, 135.4, 130.0, 129.3, 118.5, 118.4, 75.1, 73.7, 71.9, 47.3, 45.9, 45.7, 42.0, 36.6, 34.5, 34.4, 34.3, 34.19, 34.15, 33.9, 28.7, 27.2, 25.64, 25.56, 25.3, 25.1, 25.0, 23.6, 22.7, 22.3, 21.9. HRMS (ESI) (m/z): [M+1]+ calcd for $C_{25}H_{34}NO_4$: 412.2482, found: 412.2479.

Tricyclic Compound 12d: Use of the general procedure with enone **10d** (358.4 mg, 0.813 mmol) provided 299.6 mg of the pure tricyclic product as a 1:1 mixture of two epimers in an 84% yield. $[\alpha]_D^{24} = -37$ (c=0.4, CH_2Cl_2).Less polar epimer: ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 6.71-6.60 (m, 1H), 6.51-6.35 (m, 2H), 6.03-5.84 (m, 1H), 5.24-5.04 (m, 2H), 4.78-4.64 (m, 1H), 3.85 (s, 3H), 3.83-3.71 (m, 3H), 3.70-3.59 (m, 2H), 3.59-3.47 (m, 2H), 3.39-3.28 (m, 3H), 2.76-2.58 (m, 2H), 2.58-2.41 (m, 1H), 2.40-2.28 (m, 2H), 2.09-1.78 (m, 5H), 1.53-1.15 (m, 6H).More polar epimer: ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 6.82-6.54 (m, 2H), 5.94-5.76 (m, 1H), 5.14-4.93 (m, 2H), 4.42-4.17 (m, 1H), 3.90-3.79 (m, 4H), 3.79-3.73 (m, 2H), 3.68-3.23 (m, 4H), 3.22-2.96 (m, 3H), 2.96-2.82 (m, 3H), 2.53-2.40 (m, 2H), 2.33-2.06 (m, 4H), 2.02-1.84 (m, 4H), 1.83-1.44 (m, 3H). Less polar epimer: ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u 134.1, 134.0, 111.2, 111.1, 111.0, 110.4, 61.6, 61.56, 59.2, 59.1, 57.5, 56.4, 56.0, 55.9, 55.8, 40.9, 40.2, 21.0, 14.13, 14.1; δ_d 179.2, 166.8, 147.6, 147.5, 131.7, 129.0, 128.7, 118.7, 118.5, 97.5, 72.6, 72.4, 49.4, 49., 42.3, 42.1, 36.6, 36.3, 34.2, 33.9, 28.8, 27.3, 26.7, 26.6, 26.4, 26.3, 25.8, 25.5, 25.1. More polar epimer: ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u133.76, 133.69, 133.63, 113.6, 113.2, 112.5, 112.3, 111.67, 111.59, 111.52, 111.37, 61.3, 61.0, 60.94, 60.3, 59.2, 59.0, 58.8, 58.7, 57.0, 56.7, 56.5, 56.0, 55.89, 55.86, 55.82, 55.79, 55.73, 48.1, 46.8, 46.8, 46.7, 14.2; δ_d 206.91, 206.84, 26.42, 206.3, 169.1, 168.6, 168.5, 168.4, 147.78, 147.67, 147.64, 146.94, 146.90, 146.79, 146.71, 129.9, 129.7, 129.4, 128.9, 125.98, 125.95, 125.75, 125.70, 118.4, 118.3, 75.1, 73.8, 72.3, 71.5, 47.4, 47.2, 46.0, 45.9, 42.0, 41.9, 41.86, 36.7, 36.68, 36.58, 34.43, 34.36, 34.30, 34.12, 34.09, 34.0, 33.93, 33.89, 28.9, 27.3, 27.2, 25.5, 25.4, 25.3, 25.2, 25.11, 25.04, 25.01, 24.99, 23.37, 23.61, 22.3, 22.0. HRMS (ESI) (m/z): [M+1]+ calcd for $C_{26}H_{36}NO_5$: 442.2588, found: 442.2584.

Tricyclic Compound 12e: Use of the general procedure with enone **10e** (356.6 mg, 0.903 mmol) provided 251.0 mg of the pure tricyclic product as a 1:1 mixture of two epimers in a 70% yield. $[\alpha]_D^{24} = -48$ (c=0.87, CH_2Cl_2). Less polar epimer: ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 7.08-6.89 (m, 2H), 6.89-6.76 (m, 1H), 6.00-5.74 (m, 1H), 5.25-4.97 (m, 2H), 4.78-4.65 (m, 1H), 3.81-3.50 (m, 3H), 3.50-3.27 (m, 4H), 2.83-2.62 (m, 2H), 2.62-2.42 (m, 2H), 2.40-2.14 (m, 6H), 2.14-1.75 (m, 6H), 1.73-1.14 (m, 3H). More polar epimer: ^{1}H NMR ($CDCl_3$, a mixture of rotamers) δ 6.11-6.78 (m, 3H), 5.99-5.73 (m, 1H), 5.17-4.93 (m, 2H), 4.35-4.14 (m, 1H), 3.75-3.50 (m, 2H), 3.50-3.31 (m, 3H), 3.17-3.06 (m, 1H), 2.97-2.88 (m, 3H), 2.54-2.24 (m, 2H), 2.28 (s, 3H), 2.26-2.09 (m, 2H), 2.08-1.80 (m, 5H), 1.83-1.56 (m, 4H), 1.52-1.41 (m, 1H).Less polar epimer: ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u134.3, 133.7, 133.6, 130.4, 129.7, 129.6, 129.5, 129.3, 129.1, 128.7,128.5, 128.3, 127.4, 127.3, 127.2, 126.9, 126.6, 126.5, 61.6, 61.5, 61.1, 60.9, 60.7, 59.1, 59.0, 58.6, 57.0, 56.6, 47.15, 47.04, 46.8, 40.9, 40.3, 21.0, 20.9; δ_d 206.6, 178.7, 136.6, 136.5, 136.3, 136.1, 134.8, 134.0, 133.8, 118.5, 118.4, 118.3, 118.1, 73.9, 73.5, 72.4, 72.2, 71.9, 50.3, 49.2, 48.9, 47.3, 45.7, 42.2, 42.1, 42.0, 36.6, 36.3, 35.9, 34.12, 34.06, 33.8, 28.8, 28.7, 28.0, 27.3, 27.2, 27.1, 26.9, 26.6, 26.5, 26.3, 25.5, 25.4, 25.3, 25.2,25.1, 24.9, 23.6, 21.9, 19.6.More polar epimer: ^{13}C NMR ($CDCl_3$, a mixture of rotamers) δ_u133.7, 133.6, 130.3, 129.7, 129.6, 129.5, 126.7, 126.5, 60.9, 60.7, 59.0, 58.6, 57.0, 56.6, 47.1, 46.8, 21.0, 20.9; δ_d 206.98, 206.54, 168.6, 168.3, 136.2, 136.0, 134.7, 134.1, 133.94, 133.8, 118.4, 118.3, 73.5, 73.3, 47.3, 45.7, 42.1, 42.0,36.6, 34.17, 34.11, 34.05, 33.8, 28.7, 27.3, 25.5, 25.3, 25.2, 23.6, 21.9. HRMS (ESI) (m/z): [M+1]+ calcd for $C_{25}H_{34}NO_3$: 396.2533, found: 396.2530.

General Procedure for Chiral Auxiliary Removal: β-ketoamide (1.0 eq.) and N-methylhydroxylamine hydrochloride (2.0 eq.) were dissolved in EtOH (10 mL/mmol β-ketoamide). This was refluxed overnight. The next day EtOH was removed in vacuo, and the resulting residue was re-dissolved in EtOAc and water. The organic layer was separated and the aqueous layer was extracted two times more with EtOAc. The combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude isoxazolone was purified using column chromatography (EtOAc in heptanes).

Isoxazolidinone 13b: Use of the general procedure with β-ketoamide **11b** (122.0 mg, 0.307 mmol) provided 74.1 mg of the pure isoxazolidinone in a 77% yield. $[\alpha]_D^{24}$ = −113 (c=0.4, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.51-7.43 (d, 1H, *J*=3.02 Hz), 6.75-6.69 (m, 2H), 5.95-5.81 (m, 1H), 5.18-5.09 (m, 2H), 3.78 (s, 3H), 3.75 (s, 1H), 3.22 (s, 3H), 3.05-2.66 (dd, 2H, *J*=123.2, 15.76 Hz), 2.50-2.21 (m, 4H), 1.84-1.62 (m, 2H). ^{13}C NMR ($CDCl_3$) δ_u134.3, 126.2, 112.3, 110.6, 55.4, 44.2, 38.4; δ_d 171.3, 164.2, 159.1, 142.0, 136.4, 118.1, 102.7, 45.7, 42.9, 41.1, 29.7, 18.9. GC t_R = 15.23 min. EI-MS *m/z* (%): 311 (M^+, 9), 269 (100), 224 (32), 152 (20). HRMS (ESI) (m/z): [M+1]+ calcd for $C_{19}H_{22}NO_3$: 312.1594, found: 312.1591.

Isoxazolidinone 13d: Use of the general procedure with β-ketoamide **11d** (259 mg, 0.607 mmol) provided 150.2 mg of the pure isoxazolidinone in a 72% yield. $[\alpha]_D^{24}$ = −156 (c=0.53, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.16, 6.68 (two s, 2H), 5.93-5.77 (m, 1H), 5.18-5.07 (m, 2H), 3.84 (2s, 6H), 3.75 (s, 1H), 3.22 (s, 3H), 3.00-2.60 (dd, 2H, *J*=128, 19.36), 2.50-2.24 (m, 4H), 1.84-1.65 (m, 2H).^{13}C NMR ($CDCl_3$) δ_u134.4, 108.6, 108.0, 56.04, 55.98, 44.98, 38.4; δ_d 171.4, 164.3, 148.43, 148.37, 136.0, 131.8, 118.0, 102.5, 45.7, 42.8, 41.3, 28.0, 18.9. GC t_R = 13.49 min. EI-MS *m/z* (%): 341 (M^+, 52), 299 (97), 254 (79), 224 (100). HRMS (ESI) (m/z): [M+1]+ calcd for $C_{20}H_{24}NO_4$: 342.1700, found: 342.1696.

Isoxazolidinone 13e: Use of the general procedure with β-ketoamide **11e** (112.5 mg, 0.295 mmol) provided 52.6 mg of the pure isoxazolidinone in a 60% yield. $[\alpha]_D^{24}$ = −200 (c=0.27, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.52-7.41 (d, 1H, *J*=8.08 Hz), 6.99 (s, 2H), 5.98-5.80 (m, 1H), 5.20-5.06 (m, 2H), 3.78 (s, 1H), 3.23 (s, 3H), 3.05-2.95 (m, 1H), 2.74-2.64 (m, 1H), 2.50-2.36 (m, 1H), 2.36-2.26 (m, 6H), 1.84-1.62 (m, 2H). ^{13}C NMR ($CDCl_3$) δ_u 134.4, 127.7, 125.5, 125.3, 44.6, 38.4, 21.3; δ_d 171.3, 164.3, 141.2, 140.6, 136.6, 118.0, 102.7, 45.5, 42.7, 41.1, 27.6, 18.9. GC t_R = 11.21 min. EI-MS *m/z* (%): 295 (M^+, 17), 253 (100), 208 (42), 193 (36), 164 (27).HRMS (ESI) (m/z): [M+1]+ calcd for $C_{19}H_{22}NO_2$: 296.1645, found: 296.1642.

Isoxazolidinone 14b: Use of the general procedure with β-ketoamide **12b** (344.1 mg, 0.837 mmol) provided 225.6 mg of the pure isoxazolidinone in an 83% yield. $[\alpha]_D^{24}$ = −135 (c=0.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.60-7.51 (d, 1H, *J*=8.80 Hz), 6.78-6.66 (dd, 1H, *J*=8.68, 2.76 Hz), 6.63-6.58 (d, 1H, *J*=2.72 Hz), 5.95-5.81 (m, 1H), 5.20-5.03 (m, 2H), 3.76 (s, 3H), 3.47 (s, 1H), 3.23 (s, 3H), 2.87-2.68 (m, 2H), 2.48-2.28 (m, 2H), 2.24-2.01 (m, 2H), 1.88-1.73 (m, 3H), 1.60-1.51 (m, 1H). ^{13}C NMR ($CDCl_3$) δ_u 133.7, 131.0, 113.0, 112.3, 55.2, 38.4, 38.1; δ_d 172.1, 164.4, 157.8, 136.2, 129.9, 118.2, 103.9, 41.6, 35.4, 31.8, 26.0,

25.5, 19.0. GC t_R = 13.89 min. EI-MS *m/z* (%): 325 (M^+, 24), 297 (8), 283 (100), 171 (18). HRMS (ESI) (m/z): [M+1]+ calcd for $C_{20}H_{24}NO_3$: 326.1751, found: 326.1747.

Isoxazolidinone 14d: Use of the general procedure with β-ketoamide **12d** (283.6 mg, 0.643 mmol) provided 192.0 mg of the pure isoxazolidinone in an 84% yield. $[\alpha]_D^{24}$ = +4.4 (c=0.93, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.43 (s, 1H), 6.53 (s, 1H), 6.63-6.58, 5.96-5.75 (m, 1H), 5.21-4.98 (m, 2H), 3.92-3.73 (m, 6H), 3.51 (s, 1H), 3.31-3.15 (m, 3H), 2.85-2.52 (m, 2H), 2.48-2.29 (m, 2H), 2.22-2.11 (m, 1H), 2.08-1.98 (m, 1H), 1.95-1.82 (m, 2H), 1.79-1.66 (m, 1H), 1.60-1.49 (m, 1H). ^{13}C NMR ($CDCl_3$) δ_u 133.6, 112.7, 110.9, 55.9, 55.8, 38.4, 38.3; δ_d 172.4, 164.4, 147.7, 147.2, 130.0, 126.1, 118.5, 103.9, 41.6, 34.9, 32.0, 25.0, 24.8, 18.9. GC t_R = 15.23 min. EI-MS *m/z* (%): 355 (M^+, 70), 313 (100), 296 (49), 268 (50), 201 (55). HRMS (ESI) (m/z): [M+1]+ calcd for $C_{21}H_{26}NO_4$: 356.1856, found:356.1852.

Isoxazolidinone 14e: Use of the general procedure with β-ketoamide **12e** (246.3 mg, 0.624 mmol) provided 150.0 mg of the pure isoxazolidinone in a 78% yield. $[\alpha]_D^{24}$ = −149 (c=0.13, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.59-7.60 (d, 1H, *J*=7.96 Hz), 7.03-6.95 (d, 1H, *J*=7.36 Hz), 6.91 (s, 1H), 5.99-5.80 (m, 1H), 5.21-5.00 (m, 2H), 3.52 (s, 1H), 3.24 (s, 3H), 2.86-2.65 (m, 2H), 2.47-2.32 (m, 2H), 2.30 (s, 3H), 2.23-2.01 (m, 3H), 1.89-1.75 (m, 3H). ^{13}C NMR ($CDCl_3$) δ_u 133.7, 129.8, 128.9, 127.2, 38.42, 38.40, 20.9; δ_d 172.1, 164.6, 135.6, 134.9, 134.7, 118.5, 104.0, 41.6, 35.2, 31.9, 25.6, 25.4, 19.0. GC t_R = 12.33 min. EI-MS *m/z* (%): 309 (M^+, 42), 267 (100), 222 (39), 165 (42), 155 (60). HRMS (ESI) (m/z): [M +1]+ calcd for $C_{20}H_{24}NO_2$: 310.1802, found:310.1798.

General Procedure for Isoxazolidinone Cleavage: Isoxazolidinone (1.0 eq.) and $Mo(CO)_6$ (1.2 eq.) were dissolved in a 15:1 ratio of ACN:H_2O (15 mL ACN/mmol isoxazolidinone). This was refluxed overnight. The next day the reaction mixture was concentrated directly onto silica and purified via column chromatography (EtOAc in heptanes).

Ketone 15b: Use of the general procedure with isoxazolidinone **13b** (39.5 mg, 0.127 mmol) provided 28.2 mg of the pure product in an 87% yield. $[\alpha]_D^{24}$ = −68 (c=0.13, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.05-6.97 (d, 1H, *J*=9.08 Hz), 6.74-6.68 (m, 2H), 5.94-5.81 (m, 1H), 5.18-5.09 (m, 2H), 3.76 (s, 3H), 3.33-3.28 (t, 1H, *J*=5.64 Hz), 3.08-2.99 (d, 1H, *J*=16.32 Hz), 2.78-2.60 (m, 3H), 2.50-2.42 (m, 1H), 2.42-2.47 (m, 2H), 2.10-2.02 (m, 1H), 1.98-1.88 (m, 1H), 1.84-1.75 (m, 1H). ^{13}C NMR ($CDCl_3$) δ_u134.5, 124.2, 112.5, 110.3, 55.4, 48.7; δ_d 212.3, 159.3, 143.2, 136.6, 118.2, 44.7, 44.4, 44.0, 41.8, 36.4, 32.2.GC t_R = 8.55 min. EI-MS *m/z* (%): 256 (M^+, 10), 214 (100), 172 (30), 115 (26). HRMS (ESI) (m/z): [M-1]+ calcd for $C_{17}H_{19}O_2$: 255.1380, found: 255.1377.

Ketone 15d: Use of the general procedure with isoxazolidinone **13d** (150.2 mg, 0.440 mmol) provided 104.1 mg of the pure product in an 82% yield. $[\alpha]_D^{24}$ = −12 (c=0.4, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 6.69, 6.61 (two s, 2H), 5.94-5.77 (m, 1H), 5.20-5.07 (m, 2H), 3.84 (s, 6H), 3.36-3.28 (m, 1H), 3.07-2.97 (d, 1H, *J*=16.04 Hz), 2.81-2.68 (m, 2H), 2.69-2.59 (m, 1H), 2.50-2.23 (m, 3H), 2.13-2.02 (m, 1H), 2.01-1.89 (m, 1H), 1.89-1.75 (m, 1H). ^{13}C NMR ($CDCl_3$) δ_u134.4, 107.8, 106.7, 56.06, 56.03, 49.2; δ_d 212.4, 148.7, 148.6, 136.1, 133.1, 118.2, 44.55, 44.53, 44.3, 42.0, 36.2, 32.3.GC t_R = 9.52 min. EI-MS *m/z* (%):

286 (M^+, 35), 244 (100), 188 (35), 115 (26). HRMS (ESI) (m/z): [M]+ calcd for $C_{18}H_{22}O_3$: 286.1564, found: 286.1559.

Ketone 15e: Use of the general procedure with isoxazolidinone **13e** (42.7 mg, 0.145 mmol) provided 34.8 mg of the pure product in an 80% yield. $[\alpha]_D^{24}$ = −27.6 (c=0.47, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.09-6.94 (m, 3H), 6.01-5.81 (m, 1H), 5.25-5.09 (m, 2H), 3.36 (t, 1H, *J*=5.52 Hz), 3.10-3.00 (m, 1H), 2.81-2.65 (m, 3H), 2.54-2.36 (m, 2H), 2.32 (s, 4H), 2.15-2.02 (m, 1H), 2.02-1.89 (m, 1H), 1.89-1.76 (m, 1H). ^{13}C NMR ($CDCl_3$) δ_u134.5, 127.6, 125.5, 123.4, 49.1, 21.2; δ_d 212.2, 141.8, 141.6, 136.8, 118.1, 44.5, 44.2, 43.9, 21.7, 36.5, 32.1. GC t_R = 7.44 min. EI-MS *m/z* (%): 240 (M^+, 33), 197 (100), 155 (56), 127 (36). HRMS (CI) (m/z): [M+1]+ calcd for $C_{17}H_{21}O$: 241.1592, found: 241.1589.

Ketone 16b: Use of the general procedure with isoxazolidinone **14b** (225.6 mg, 0.694 mmol) provided 167.6 mg of the pure product in a 90% yield. $[\alpha]_D^{24}$ = +21.5 (c=0.87, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 6.99-6.88 (d, 1H, *J*=8.36 Hz), 6.76-7.70 (dd, 1H, *J*=8.40, 2.72 Hz), 6.69-6.66 (d, 1H, *J*=2.60 Hz), 5.95-5.75 (m, 1H), 5.18-4.95 (m, 2H), 3.79 (m, 3H), 2.98-2.87 (m, 2H), 2.85-2.76 (m, 1H), 2.52-2.40 (m, 3H), 2.37-2.28 (m, 1H), 2.28-2.20 (m, 1H) 2.00-1.79 (m, 3H), 1.65-1.54 (m, 2H). ^{13}C NMR ($CDCl_3$) δ_u 133.8, 130.0, 113.8, 112.4, 55.2, 45.3; δ_d 211.5, 158.0, 135.6, 130.9, 118.1, 47.7, 41.9, 37.1, 33.3, 34.4, 25.8, 25.1. GC t_R = 9.43 min. EI-MS *m/z* (%): 270 (M^+, 32), 228 (100), 199 (18), 171 (27). HRMS (CI) (m/z): [M+1]+ calcd for $C_{18}H_{23}O_2$: 271.1698, found: 271.1698.

Ketone 16d: Use of the general procedure with isoxazolidinone **14d** (192.0 mg, 0.541 mmol) provided 133.9 mg of the pure product in an 82% yield. $[\alpha]_D^{24}$ = +73 (c=0.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 6.61 (s, 1H), 6.49 (s, 1H), 5.96-5.72 (m, 1H), 5.17-4.96 (m, 2H), 3.93-3.76 (m, 6H), 2.93-2.80 (m, 2H), 2.80-2.72 (m, 1H), 2.56-2.40 (m, 3H), 2.39-2.11 (m, 3H), 1.98-1.83 (m, 3H), 1.63-1.54 (m, 1H). ^{13}C NMR ($CDCl_3$) δ_u 133.8, 111.7, 111.6, 55.9, 55.8, 45.8; δ_d 211.6, 147.6, 147.5, 130.6, 126.0, 118.3, 47.9, 41.8, 37.1, 35.3, 34.3, 25.2, 25.0. GC t_R = 10.38 min. EI-MS *m/z* (%): 300 (M^+, 100), 258 (87), 201 (63), 151 (57). HRMS (CI) (m/z): [M]+ calcd for $C_{19}H_{24}O_3$: 300.1725, found: 300.1713.

Ketone 16e: Use of the general procedure with isoxazolidinone **14e** (138.1 mg, 0.447 mmol) provided 138.1 mg of the pure product in a 70% yield. $[\alpha]_D^{24}$ = +78.5 (c=0.2, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.03-6.87 (m, 3H), 5.97-5.75 (m, 1H), 5.20-4.97 (m, 2H), 3.97-3.78 (m, 3H), 2.53-2.40 (m, 3H), 2.39-2.33 (m, 1H), 2.32 (s, 3H), 2.30-2.15 (m, 2H), 2.00-1.81 (m, 3H), 1.68-1.57 (m, 1H). ^{13}C NMR ($CDCl_3$) δ_u 133.9, 129.8, 129.0, 127.1, 45.6, 21.0; δ_d 211.5, 135.8, 135.7, 134.1, 118.1, 48.1, 42.0, 37.0, 35.2, 34.3, 25.26, 25.19. GC t_R = 8.45 min. EI-MS *m/z* (%): 254 (M^+, 9), 212 (100), 155 (65), 141 (45), 128 (44). HRMS (CI) (m/z): [M+1]+ calcd for $C_{18}H_{23}O$: 255.1749, found: 255.1737.

General Procedure for Regioselective Enol Silane Formation: Chiral amine, (+)-bis[(R)-1-phenethyl]amine (2.0 eq.), was dissolved in toluene and the mixture was cooled to −78°C. Next n-BuLi (2.0 eq.) was added, and the reaction was stirred at this temperature for 30 min. HMPA (2.0 eq.) was added, and at this point the reaction turned a pink/peach color. The reaction was warmed to room temperature, recooled to −78°C, and TBS-OTf (5.0 eq.) was added followed by the addition of ketone (1.0 eq.) dropwise. The reaction then became

a cloudy opaque white color, and was stirred overnight while warming to room temperature. The next day the reaction was quenched with Et_3N and saturated $NaHCO_3$. The aqueous layer was extracted 3× with ether and the combined organics were washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified via column chromatography (EtOAc in heptanes). HRMS and optical rotations were not determined as the enol silanes were susceptible to decomposition and therefore were used soon after isolation.

Enol Silanes 17 and 18: Use of the general procedure with ketone **15d** (64.6 mg, 0.226 mmol) provided 82.0 mg of pure product as a mixture of regioisomers in ~2.5:1 ratio by ^{1}H NMR, a 91% yield. ^{1}H NMR ($CDCl_3$) δ 6.76, 6.72, 6.68 (3s, 2H), 5.98-5.82 (m, 1H), 5.21, 5.19 (d, 0.30H, *J* = 5.08 Hz), 5.14-5.05 (m, 2H), 4.78-4.73 (br, 0.67H), 3.88 (s, 3H), 3.86 (s, 3H), 3.38-3.05 (m, 1H), 2.90-2.70 (m, 1H), 2.59-2.11 (m, 5H), 2.00-1.80 (m, 2H), 0.97-0.83 (m, 9H), 0.22-0.054 (m, 6H). GC t_R = 10.54 min. (Major regioisomer, 66%) EI-MS *m/z* (%): 400 (M^+, 19), 358 (16), 269 (100), 216 (34). t_R = 10.57 min. (Major regioisomer, 33%) EI-MS *m/z* (%): 400 (M^+, 19), 358 (100), 327 (16), 269 (10), 227 (16).

Enol Silanes 19 and 20: Use of the general procedure with ketone **16b** (73.2 mg, 0.271 mmol) provided 98.4 mg of pure product as a mixture of regioisomers in ~4:1 ratio by ^{1}H NMR, a 95% yield. ^{1}H NMR ($CDCl_3$) δ 7.22-7.05 (m, 1H), 7.03-6.94 (m, 1H), 6.77-6.63 (m, 1H), 5.97-5.75 (m, 1H), 5.14-5.92 (m, 2H), 5.92-4.77 (m, 1H), 3.80 (s, 3H), 2.93-2.60 (m, 2H), 2.32-1.79 (m, 7H), 1.49-1.36 (m, 1H), 1.00-0.82 (m, 9H), 0.19-0.057 (m, 6H). GC t_R = 10.43 min. (Minor regioisomer, 18.5%) EI-MS *m/z* (%): 384 (M^+, 12), 342 (71), 327 (18), 253 (23), 210 (75), 72 (100). t_R = 10.51 min. (Major regioisomer, 66.3%) EI-MS *m/z* (%): 384 (M^+, 6), 253 (100), 210 (51), 72 (24).

Bicyclo[3.2.1]octane 21: Enol silanes **17** and **18** (58.9 mg, 0.147 mmol) were dissolved in DMSO (3 mL) and $Pd(OAc)_2$ (3 mg, 0.013 mmol) was added. The reaction mixture was then put under an oxygen atmosphere and heated to 45°C overnight. Upon completion, as determined by TLC, the reaction was concentrated under reduced pressure, loaded directly onto silica gel and purified via column chromatography (1:10 EtOAc/heptanes). The desired cyclized product **21** was isolated as a 15.4 mg sample, which was a mixture of **21:23:18** in an 88:5:6 ratio (see GC analysis), which amounts to a 41% yield of **21**. Further chromatographic purification afforded a pure 2.5 mg (8% yield) sample which was used for characterization purposes. $[\alpha]_D^{24}$ = +44.5 (c=0.4, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) 6.74 (s, 1H), 6.60 (s, 1H) 5.22 (s, 1H), 5.09 (s, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.34-3.26 (d, 1H, *J*=4.56 Hz), 3.24-3.08 (m, 2H), 2.98-2.78 (m, 2H), 2.71-2.59 (dt, 1H, *J*=18.84, 2.92 Hz), 2.57-2.39 (m, 2H), 2.08-2.00 (dd, 1H, *J*=12.12, 12.16 Hz), 1.80-1.71 (dd, 1H, *J*=12.12, 12.48 Hz). ^{13}C NMR ($CDCl_3$) δ 209.1, 148.6, 146.3, 137.5, 133.2, 111.1, 107.8, 106.8, 57.6, 56.1, 50.8, 47.4, 44.5, 41.0, 40.2, 37.0. GC t_R = 9.49 min. (Minor regioisomer, 5%) EI-MS *m/z* (%): 284 (M^+, 50), 242 (100), 227 (2), 128 (15). GC t_R = 9.97 min. (Desired product, 88%) EI-MS *m/z* (%): 284 (M^+, 100), 242 (50), 189 (24), 115 (23). GC t_R = 10.73 min. (Residual enol silane, 6%) EI-MS *m/z* (%): 400 (M^+, 15), 358 (100), 327 (11), 227 (17), 73 (25). HRMS (CI) (m/z): [M]+ calcd for $C_{18}H_{20}O_3$: 284.1412, found: 284.1412.

Bicyclo[3.2.1]octane 25–28: Enol silanes **19** and **20** (98.4 mg, 0.256 mmol) were dissolved in DMSO (5 mL) and $Pd(OCOCF_3)_2$ (12 mg, 0.036 mmol) was added. The reaction mixture was then put under an oxygen atmosphere and heated to 45°C overnight. The reaction was monitored by TLC and upon completion concentrated under reduced pressure, loaded directly onto silica gel and purified via column chromatography (1:19 EtOAc/heptanes). A 41.1 mg mixture of **25:26:27:28** in a 46:31:15:8 ratio was obtained (60% yield of the four isomers). ^{1}H NMR ($CDCl_3$) δ 7.23-6.91 (3 sets of doublets, 1 H, *J*=8.6 Hz), 6.81-6.62 (m, 2H), 5.89-5.84 (d, 0.078 H, *J*=1.64 Hz), 5.67-5.61 (d, 0.32 H, *J*=1.2 Hz), 5.22-4.99 (4s, 2H), 3.83-3.73 (m, 3H), 3.26-2.46 (m, 5H), 2.10-1.65 (m, 5H). GC t_R = 8.87 min. (Minor regioisomer, 6.7%) EI-MS *m/z* (%): 268 (M^+, 64), 253 (24), 240 (83), 212 (100), 197 (46). GC t_R = 9.22 min. (Minor regioisomer, 1.2%) EI-MS *m/z* (%): 268 (M^+, 100), 228 (39), 211 (47), 159 (47). GC t_R = 9.30 min. (Major regioisomer, 45.7%) EI-MS *m/z* (%): 268 (M^+, 93), 240 (21), 225 (40), 212 (100), 92. GC t_R = 9.59 min. (Minor regioisomer, 45.3%) EI-MS *m/z* (%): 268 (M^+, 90), 226 (100), 210 (34), 173 (34), 115 (27).

Bicyclo[3.2.1]octane 26: A mixture of alkene isomers **25–28** (46.9 mg, 0.175 mmol) was refluxed for 3 hours with $pTsOH{\cdot}H_2O$ (4.0 eq.) in benzene (50 mL/mmol alkene isomers). Once GC-MS indicated that a complete reaction had occurred, the reaction was diluted with ether and washed with saturated $NaHCO_3$. The aq. layer was extracted 3× with ether, and the combined organics were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to provide the crude product which was purified via column chromatography (10% EtOAc in heptanes) to afford 34.6 mg 74% yield) of compound **26**. $[\alpha]_D^{24}$ = −209 (c=0.27, CH_2Cl_2). ^{1}H NMR ($CDCl_3$) δ 7.06, 7.04 (d, 1H, *J*=8.6 Hz), 6.80-6.74 (dd, 1H, *J*=8.52, 2.64 Hz), 6.66, 6.65 (d, 1H, *J*=2.56 Hz),5.66-5.61 (br, 1H), 3.80 (s, 3H), 3.21-3.11 (m, 1H), 3.11-3.04 (m, 1H), 2.92, 2.91 (d, 1H, *J*=4.44 Hz), 2.90-2.81 (m, 1H), 2.77-2.68 (m, 1H), 2.64-2.55 (dd, 1H, *J*=17.5, 4.8 Hz), 2.21, 2.18 (d, 1H, *J*=11.2 Hz), 2.02-1.85 (m, 2H), 1.85-1.81 (m, 1H), 1.804, 1.801 (d, 3H, *J*=1.44 Hz). ^{13}C NMR ($CDCl_3$) δ_u137.5, 128.7, 113.3, 112.7, 59.6, 55.2, 39.8, 15.1; δ_d 206.8, 157.4, 139.8, 137.3, 132.4, 47.0, 43.8, 38.5, 32.0, 27.0. GC t_R = 9.316 min. EI-MS *m/z* (%): 268 (M^+, 100), 240 (39), 225 (82), 211 (45), 93 (27). HRMS (CI) (m/z): [M]+ calcd for $C_{18}H_{21}O_2$: 269.1542, found: 269.1539.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

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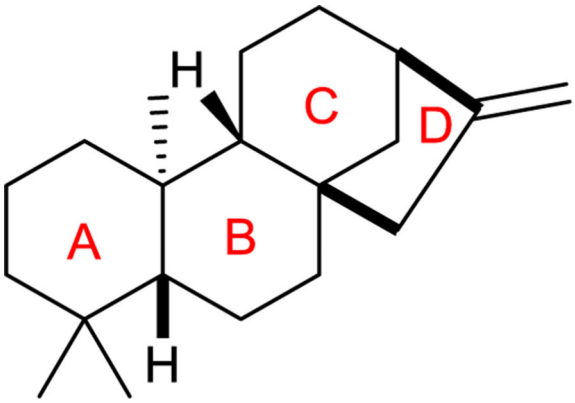
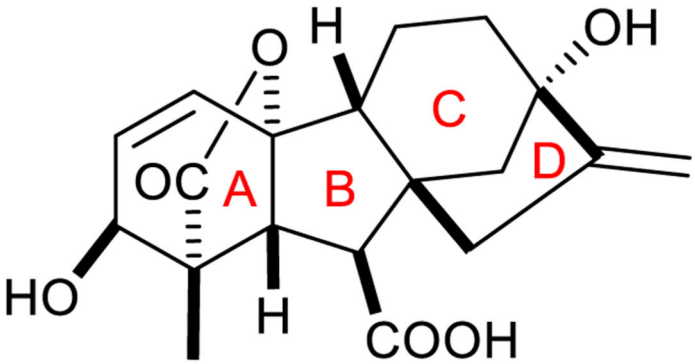


ent-kaurane



gibberellin A_3

Figure 1.
Structures of *ent*-kaurane skeleton and a gibberellin.

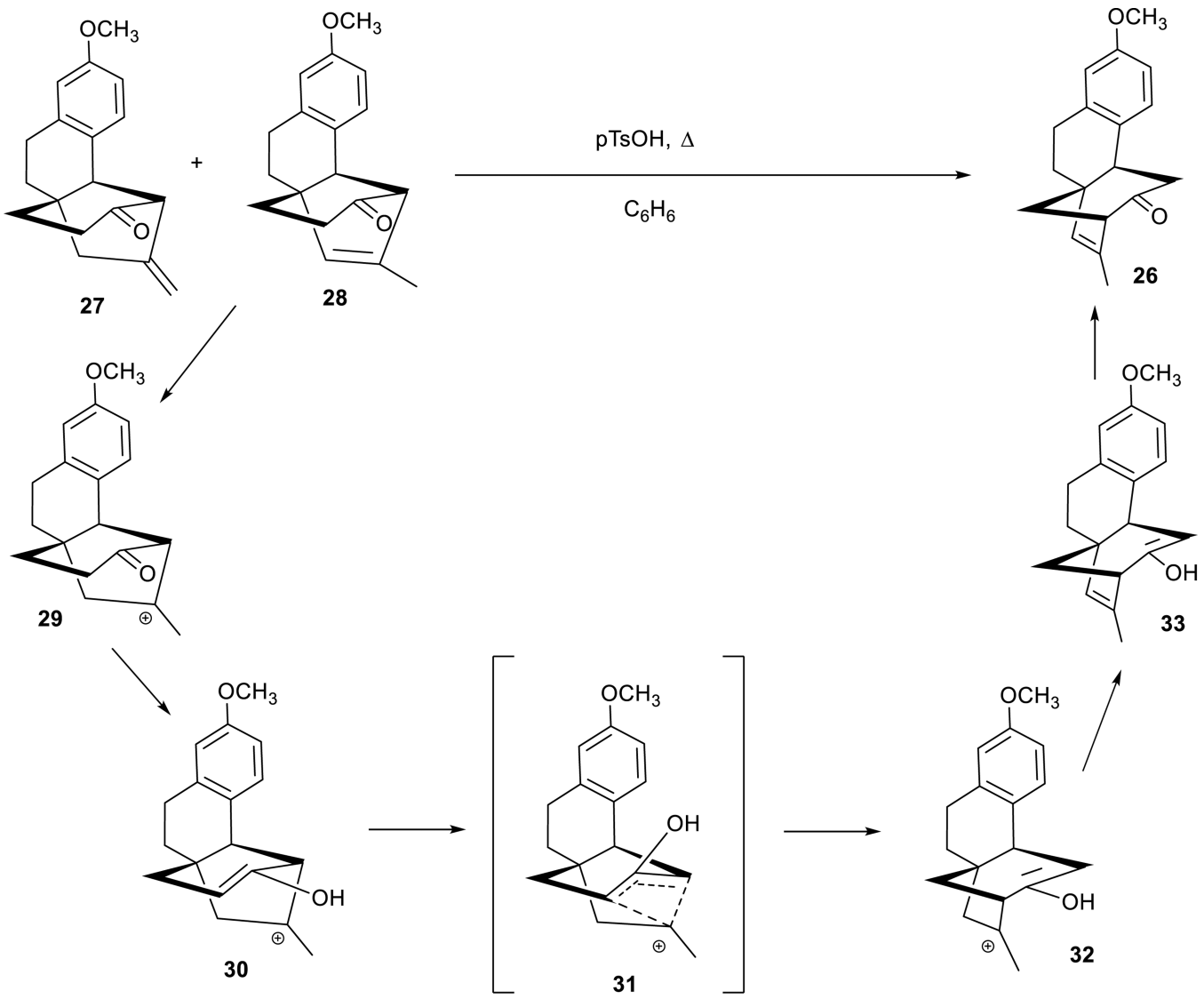
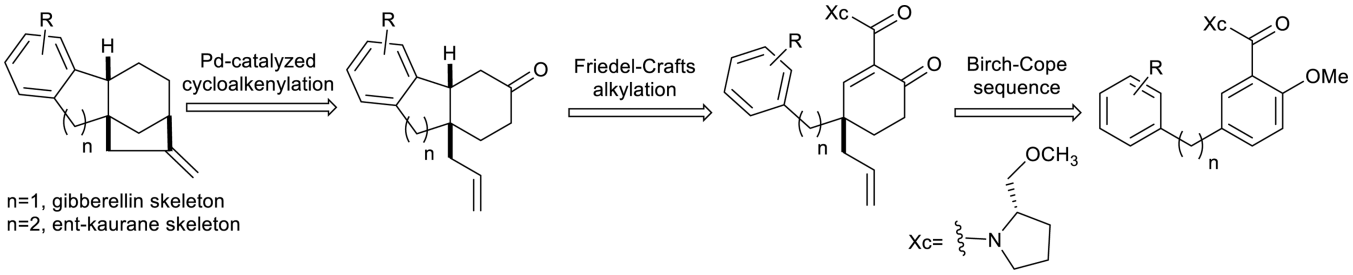


Figure 2.
Possible pathway for rearrangement of **27**/**28** into **26**

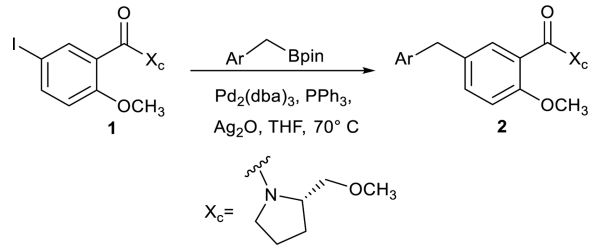


Scheme 1.

Retrosynthetic Plan for the Construction of the Gibberellin and *ent*-Kaurane Skeletons

Table 1

Synthesis of Diarylmethane Starting Materials

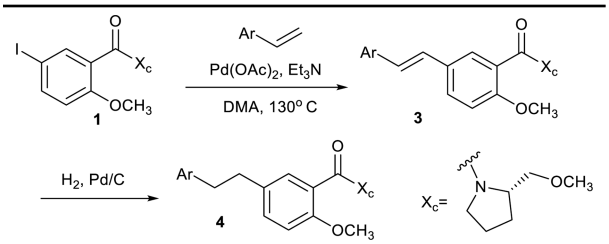


Ar	Product	% Yield
C_6H_5-	**2a**	84
3-MeO-C_6H_5-	**2b**	58
4-MeO-C_6H_5-	**2c**	61
3,4-$(MeO)_2C_6H_5$-	**2d**	56[a]
3-Me-C_6H_5-	**2e**	47

[a] Coupling conditions: $Pd(OAc)_2$, SPhos, K_2CO_3, DMF, 60° C

Table 2

Synthesis of Diarylethane Starting Materials

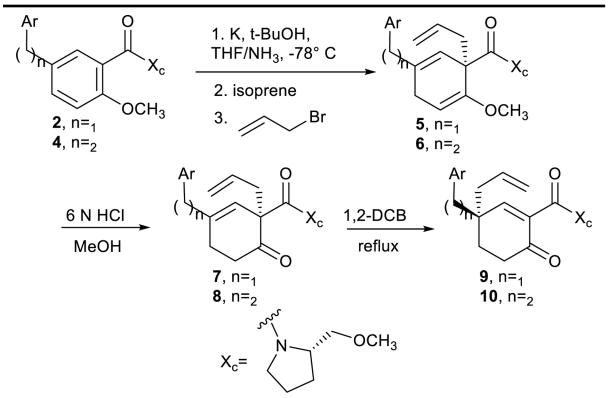


Ar	Product	% Yield	Product	% Yield
C_6H_5-	**3a**	76[a]	**4a**	90
3-MeO-C_6H_5-	**3b**	95	**4b**	83
4-MeO-C_6H_5-	**3c**	86	**4c**	87
3,4-$(MeO)_2C_6H_5$-	**3d**	88	**4d**	88
3-Me-C_6H_5-	**3e**	88	**4e**	85

[a]Conditions: $Pd(OAc)_2$, K_2CO_3, N,N-dimethyl-β-alanine, NMP[50]

Table 3

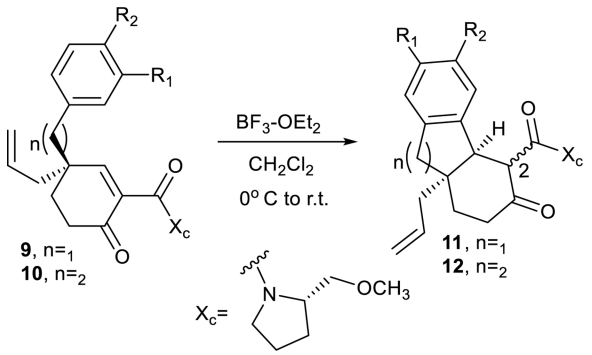
Birch-Cope Sequence



Reactant	Ar/n	Product / % Yield		
2a	C_6H_5-/1	**5a**/48	**7a**/87	**9a**/59
2b	3-MeO-C_6H_5-/1	**5b**/46	**7b**/75	**9b**/59
2c	4-MeO-C_6H_5-/1	**5c**/70	**7c**/90	**9c**/80
2d	3,4-$(MeO)_2C_6H_5$-/1	**5d**/72	**7d**/85	**9d**/73
2e	3-Me-C_6H_5-/1	**5e**/61	**7e**/62	**9e**/69
4a	C_6H_5-/2	**6a**/97	**8a**/90	**10a**/75
4b	3-MeO-C_6H_5-/2	**6b**/73	**8b**/70	**10b**/76
4c	4-MeO-C_6H_5-/2	**6c**/67	**8c**/81	**10c**/63
4d	3,4-$(MeO)_2C_6H_5$-/2	**6d**/72	**8d**/89	**10d**/72
4e	3-Me-C_6H_5-/2	**6e**/78	**8e**/94	**10e**/84

Table 4

Intramolecular Friedel-Crafts Alkylation

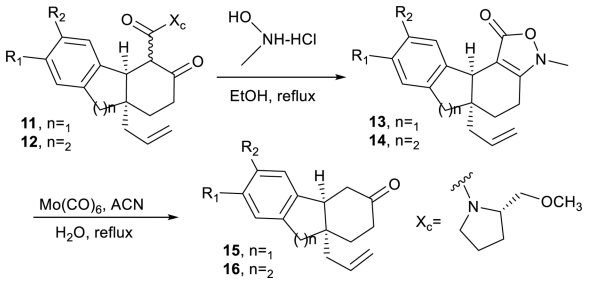


Reactant	n	R_1	R_2	Product	% Yield
9a	1	H	H	**11a**	dec.
9b	1	OCH_3	H	**11b**	98*
9c	1	H	OCH_3	**11c**	dec.
9d	1	OCH_3	OCH_3	**11d**	97*
9e	1	CH_3	H	**11e**	76*
10a	2	H	H	**12a**	63
10b	2	OCH_3	H	**12b**	88*
10c	2	H	OCH_3	**12c**	dec.
10d	2	OCH_3	OCH_3	**12d**	84*
10e	2	CH_3	H	**12e**	70*

*Product was obtained as a mixture of C-2 epimers; dec=decomposed

Table 5

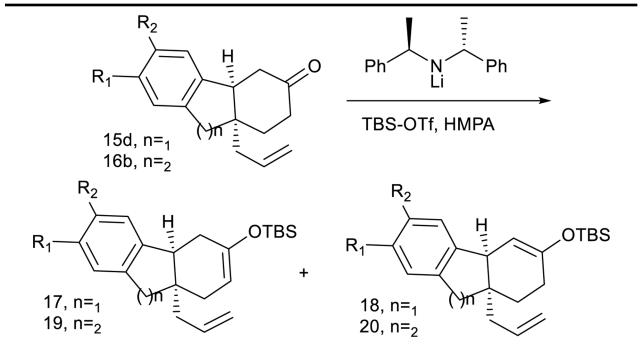
Chiral Auxiliary Removal



Reactant	N	R_1	R_2	Product / % Yield	Product / % Yield
11b	1	OCH_3	H	**13b**/77	**15b**/86
11d	1	OCH_3	OCH_3	**13d**/72	**15d**/82
11e	1	CH_3	H	**13e**/60	**15e**/80
12b	2	OCH_3	H	**14b**/83	**16b**/89
12d	2	OCH_3	OCH_3	**14d**/84	**16d**/82
12e	2	CH_3	H	**14e**/77	**16e**/70

Table 6

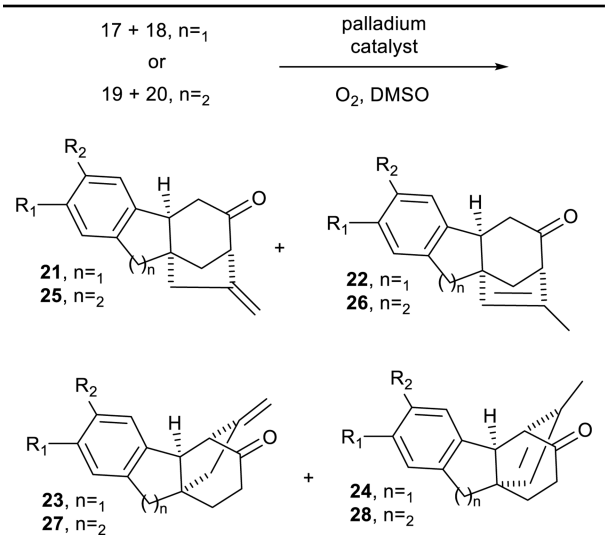
Enol Silane Formation



Reactant	n	R_1	R_2	Product	% Yield (regioselectivity)
15d	1	OCH_3	OCH_3	**17, 18**	91 (2.5:1)
16b	2	OCH_3	H	**19, 20**	95 (4:1)

Table 7

Palladium-catalyzed Cycloalkenylation



Reactant	Palladium catalyst	Product	% Yield
17, 18	$Pd(OAc)_2$	**21**	41
19, 20	$Pd(OCOCF_3)_2$	**25–28**	60 (46:31:15:8 ratio)