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A Copper-Mediated Conjugate Addition Approach to Analogues of Aconitine-Type Diterpenoid Alkaloids

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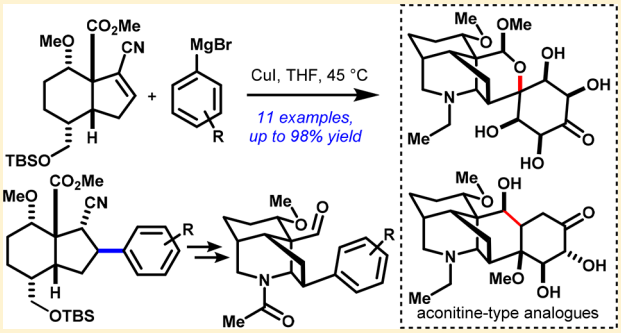
Supporting Information

ABSTRACT: A copper-mediated conjugate addition of electron-rich aryl groups into a complex vinyl nitrile using arylmagnesium bromides is reported. The conjugate addition adducts were advanced toward the synthesis of designed aconitine-type analogues. The variation in oxygenation patterns on the arene coupling partner, introduced through the current conjugate addition approach, may ultimately provide insight into structure−activity relationships of the diterpenoid alkaloids.



Aconitine (**1**, Figure 1) and lappaconitine (**2**) elicit contrasting effects upon interaction with human voltage-gated sodium ion channels; aconitine exposure induces persistent activation of neurons leading to cardiac arrest, whereas lappaconitine leads to blockage of acute pain signals.[1,2] These two related diterpenoid alkaloids exemplify the disparate effects of this class of natural products on voltage-gated ion channels.[3−6] Given that voltage-gated sodium (Na_V), calcium (Ca_V), and potassium (K_V) ion channels regulate biophysical responses across the nervous, circulatory, and muscular systems, the ability to selectively target voltage-gated sodium ion channels would have significant implications for the treatment of epilepsy, chronic pain, and myriad other channelopathies.[7]

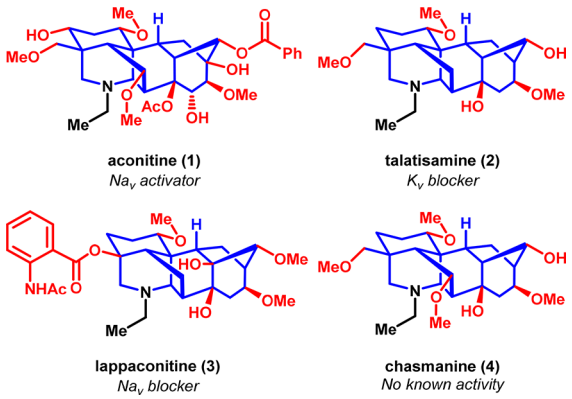


Figure 1. Selected examples of diterpenoid alkaloids.

Diterpenoid alkaloids have long been recognized for their utility in combating channelopathies, appearing in traditional Chinese medicine as treatments for pain and cardiovascular disease.[6] Today, lappaconitine (**3**) is approved and marketed in China and Russia for pain relief and arrhythmia treatment,[8] effects which likely stem from lappaconitine blocking Na_V channels.[9] On the other hand, aconitine (**1**) is a highly toxic Na_V channel activator reported to be lethal to humans in doses as low as 1−2 mg.[10] Talatisamine (**2**) is a known K_V channel blocker, whereas chasmanine (**4**) has no known ion channel activity.[4,11]

The pronounced biological effects of small changes to the periphery of these pseudoalkaloids have made the structural origin of their bioactivities a matter of interest for over a century. Among the first to explore the structure−activity relationships (SAR) of the diterpenoid alkaloids were Cash and Dunstan, who compared aconitine to two hydrolyzed derivatives, aconine and 14-*O*-benzoylaconine.[12] More recently, Tursunkhodzhaeva and co-workers probed these relationships with a larger set of isolated diterpenoid alkaloids and their derivatives.[13,14] This approach led to the identification of some key substituents on aconitine-type and lappaconitine-type natural products that imbue them with certain biological activities, but this study was limited by its inability to systematically vary the peripheral substituents. Not all combinations of substitution patterns are present in the known diterpenoid alkaloids and derivatization has been limited to hydrolysis of amides and to acylation—or, in one case, methylation—of free hydroxy groups. Furthermore, lack of site selectivity for acylation in the presence of multiple hydroxy groups has limited the synthesis of derivatives.

Our lab has developed strategies to access several C_{18}-, C_{19}-, and C_{20}-diterpenoid alkaloids.[15−17] While these efforts yielded

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enough material for biological assays, the syntheses are relatively long and opportunities for wide-ranging introduction of oxygenation have been limited. In order to overcome these challenges, we explored a synthesis approach to aconitine-type analogues that should be more amenable to systematic variation of oxygenation patterns. In designing these analogues, we generated a set of key considerations on the basis of which structural features are conserved and which are varied across this family of natural products (Figure 2).

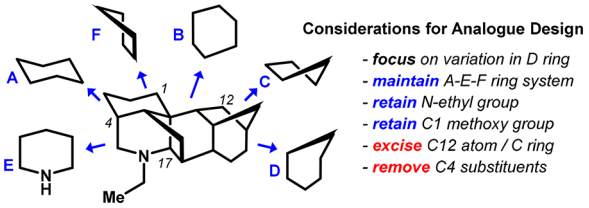


Figure 2. Ring labeling and analogue design considerations.

Previous SAR studies have indicated that variation in hydroxylation along the D ring has a drastic impact on the biological activity of aconitine-type diterpenoid alkaloids.[13,14] The primary emphasis of our design strategy thus focuses on varying the substitution pattern around this ring, while maintaining selected features common to the aconitine-type natural products. To this end, our analogues were designed to retain the A−E−F ring carbon framework, which—unlike the [3.2.1] bicycle comprised by the C and D rings—is conserved across the majority of the atisane-derived alkaloids. The *N*-ethyl group and the C1 methoxy group are also highly conserved within this family and thus maintained in our designs for analogues. C4 substituents, however, differ greatly between aconitine- and lappaconitine-type diterpenoid alkaloids. To facilitate a thorough exploration of the importance of the D ring substitution patterns, the C4 substituents were excluded from our present study, although these C4 substituents may be incorporated at a later stage using previously established strategies.[17] Additionally, diterpenoid alkaloids bearing a [2.2.2] bicycle as their CD ring system, a change which significantly alters the conformation of the D ring compared to that of the aconitine system, are also known to modulate ion channels.[18] Therefore, our initial studies aimed to excise C12 as this structural simplification would allow more rapid access to natural product-inspired analogues that probe the tolerability of the binding site to modulations in polarity, shape and spatial orientation in the D ring.

On the basis of these considerations, we targeted analogues, such as pentacycle **5** and spirocycle **6** (Figure 3). Each of these designed targets could ultimately arise from aldehyde **7** through oxidative dearomatization strategies. Aldehyde **7**, in turn, could be taken back to primary amide **8**, which itself could be derived from known vinyl nitrile **9**.[15] In the forward sense, this route would begin with a conjugate addition of aryl nucleophiles into **9**. Additional analogues could be accessed through variation of the nucleophile in this step, resulting in differing oxygenation patterns on the aryl ring (see Table 1) prior to oxidative dearomatization.

Our initial approach toward these simplified analogues was to effect a Hayashi-type[19] Rh-catalyzed conjugate addition of boronate esters into vinyl nitrile **9**, following previously successful protocols from our laboratories. However, this reaction proved to be sensitive to the electronics and substitution

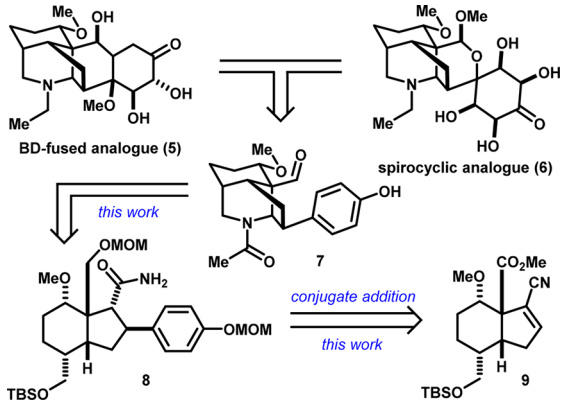
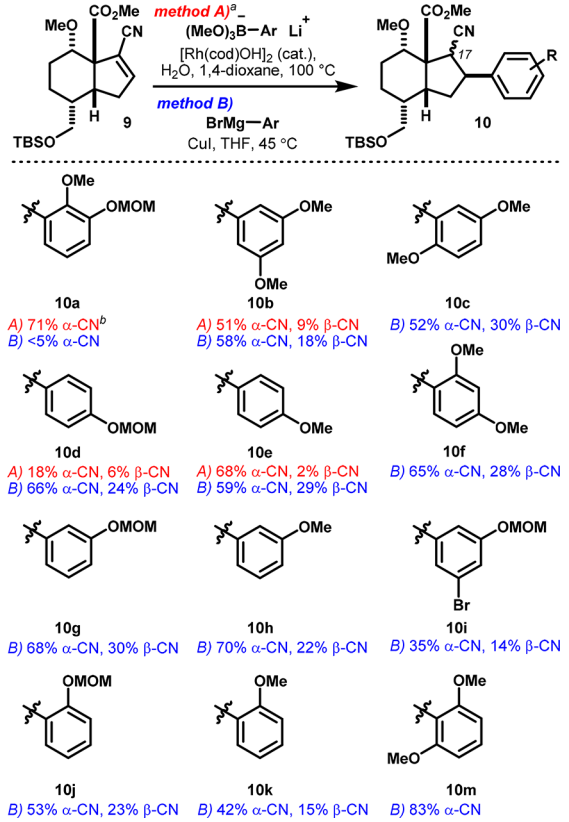


Figure 3. Retrosynthesis of two classes of aconitine analogues.

Table 1. Scope and Comparison of Rh-Catalyzed and Cu-Mediated Methods for Conjugate Addition



[a]Procedure taken from previous report; see ref 17. [b]Small amounts of *β*-CN diastereomer obtained but not characterized.

patterns of the arene nucleophiles. While the Rh-catalyzed method worked well for the two previously published substrates (Table 1, **10a** and **10b**), the same was not true when the boronate derived from MOM-protected *p*-bromophenol was used (see **10d**, Method A). In the latter case, low conversion (67% recovery of nitrile **9**) was observed.

To address the poor reactivity of many substituted aryl boronate esters in the Rh(I)-catalyzed conjugate addition, we investigated an organocuprate-based strategy using copper(I) iodide and Grignard reagents (Method B). While the conditions that were initially selected followed related precedent involving addition of alkyl cuprates into simple—and often highly activated—vinyl nitriles,[20−23] high yields using structurally complex vinyl nitrile **9** were only realized after extensive

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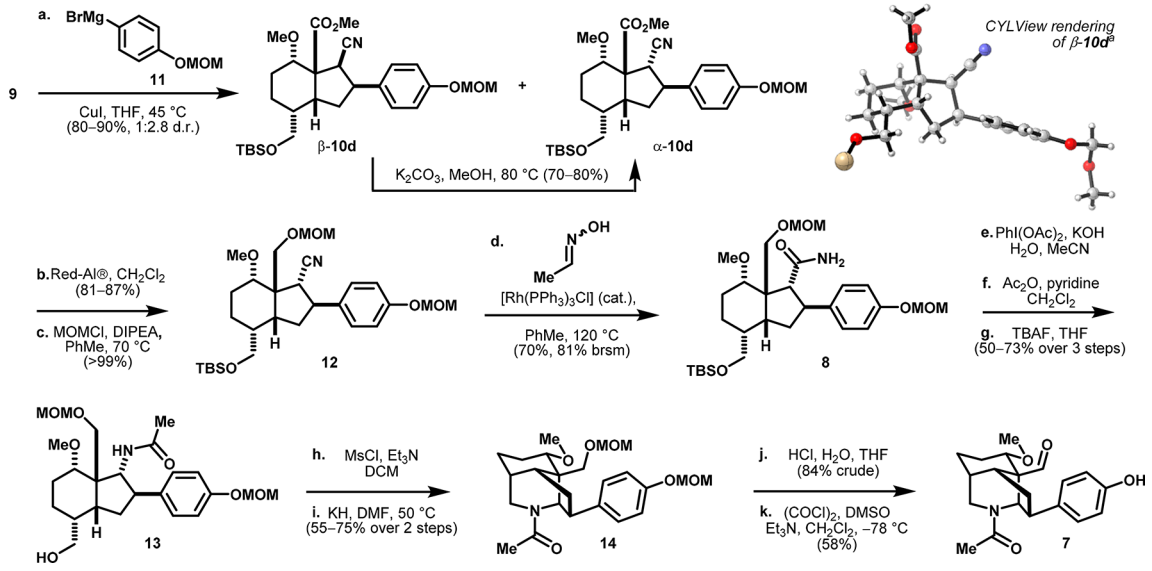
Scheme 1. Formation of Caged Piperidine Skeleton



[a]Substituents on the silicon atom omitted for clarity in CYLView rendering of the crystal structure of *β*-**10d**.

optimization. Our Cu-mediated conjugate addition method proceeded under milder conditions than the Rh-catalyzed approach and gave the desired product (**10d**) with improved efficiency over the Rh-catalyzed conjugate addition conditions (see **10d**, Method A). While a mixture of diastereomers were obtained (2.8:1 d.r. at C17), the undesired *β*-isomer could be readily epimerized using base to the desired *α*-isomer (vide infra). In order to facilitate syntheses of analogues related to **5** and **6** with a variety of substitution patterns, we explored a series of Cu-mediated conjugate additions using various oxygenated arenes. The reaction proved to be robust, tolerating a variety of substitution patterns, including sterically hindered arenes. While the use of *o*,*m*-disubstituted arenes (**10a**) resulted in low conversion, the reaction proceeded in good to excellent yield when other doubly oxygenated arenes with at least one *o*-substituent were used (**10c**, **10f**, **10m**). The conjugate addition also accommodated various phenols masked as MOM ethers (**10d**, **10g**, **10j**). Additionally, the method worked in the presence of a dibromoarene (see **10i**), allowing one of the bromine atoms to be preserved as a functional handle for further derivatization.

The conjugate addition products could then be elaborated to the caged scaffold conserved between the bioactive diterpenoid alkaloids. A synthesis of aldehyde **7** (Scheme 1) is illustrative of our approach to the common aldehyde intermediates required to generate aconitine-type analogues. Starting from vinyl nitrile **9**, conjugate addition of the cuprate derived from arylmagnesium bromide **11** afforded **10d** as a mixture of diastereomers, which were separated by flash column chromatography. The minor *β*-CN product (*β*-**10d**) was converted to the desired *α*-CN diastereomer (*α*-**10d**) under basic conditions. The structure of nitrile *β*-**10d** and the configuration of the two newly installed stereocenters relative to the rest of the hydrindane system were unambiguously confirmed by X-ray crystallography.

At this stage, the ester moiety of *α*-**10d** was reduced with Red-Al and the resultant alcohol was protected as a MOM ether to give **12**. This allowed us to retain the hydroxy group as a functional handle, in contrast to our previous syntheses, where the primary alcohol was converted to a terminal olefin.[15−17] The nitrile group was then hydrated under anhydrous conditions to afford primary amide **8**. A Hofmann rearrangement of this amide afforded a primary amine, which was subsequently acetylated to form an acetamide. In previous syntheses, a methyl carbamate had instead been installed on related substrates at this stage. This necessitated late-stage conversion of that carbamate into an acetamide. Strategies to do so required hydrolysis and decarboxylation, which generally required harsh reaction conditions. We surmised that the severe conditions for these steps would likely be problematic in the current synthesis due to the presence of free hydroxy groups in our late-stage intermediates. Thus, given that we would eventually require an acetamide—that would ultimately be reduced to the ethylamine present in our designed analogues—we decided to convert amide **8** directly to an acetamide. Following acetylation, TBAF-mediated cleavage of the TBS group gave alcohol **13**. Mesylation of the primary hydroxy group in **13** set the stage for cyclization to form piperidine **14** under basic conditions, completing the caged left-hand side of the molecule. The two MOM groups on **14** were then cleaved and the newly revealed primary hydroxy group was oxidized under Swern conditions to give aldehyde **7**.

The exploration of various cyclization modes of key intermediate **7** to the aconitine-type analogues is ongoing in our laboratories. Preliminary studies toward the spirocyclic analogues are particularly promising, and the desired scaffold (**15**) is formed through oxidative dearomatization with $PhI(OAc)_2$ in the presence of methanol (Scheme 2).[31] Efforts toward intermolecular oxidative dearomatization en route to the BD-fused analogues are also underway.

In summary, with a route to aldehyde **7** firmly established through our development of a robust and versatile conjugate addition protocol, the stage is now set for the exploration of aconitine-type analogues related to BD-fused **5** and spirocyclic **6**, which may provide additional insight into the structure−activity relationship of these intriguing pseudoalkaloids.

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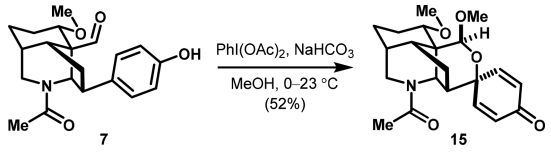
Scheme 2. Oxidative Dearomatization of 7 To Build Spirocyclic Scaffold



EXPERIMENTAL SECTION

General Experimental Methods. *1. Solvents and Reagents.* Unless noted below, commercial reagents were used without additional purification. Tetrahydrofuran (THF), diethyl ether (Et_2O), acetonitrile (MeCN), benzene, methanol (MeOH), and triethylamine (Et_3N) were sparged with argon and dried by passing through alumina columns using argon in a Glass Contour solvent purification system. Dichloromethane (CH_2Cl_2) was freshly distilled over calcium hydride under a N_2 atmosphere prior to each use. DMSO and toluene (PhMe) were distilled over calcium hydride under a N_2 atmosphere, degassed using freeze−pump−thaw (3 cycles), and stored over 4 Å molecular sieves in a Schlenk flask under N_2. Dimethylformamide (DMF), acetone, *n*-BuLi solution, LiHMDS solution, Red-Al solution, Grignard solutions, and pyridine were purchased in Sure-Seal, AcroSeal, or ChemSeal bottling, and used directly. 1,4-Dioxane was purchased in AcroSeal bottling (99.5%, anhydrous, stabilized, over 4 Å molecular sieves) and additionally sparged with N_2 prior to use.

2. Reaction Setup, Progress Monitoring, and Product Purification. Unless otherwise noted in the experimental procedures, reactions were carried out in flame or oven-dried glassware under a positive pressure of N_2 in anhydrous solvents using standard Schlenk techniques. Reactions run at temperatures above rt (22−23 °C) were controlled by an IKA temperature modulator and monitored using liquid-in-glass thermometers. Reaction progress was monitored using a combination of LC/MS analysis (Shimadzu LC−MS-2020 (UFLC) equipped with the LC20AD solvent delivery system, a SPD-20AV prominence UV−vis detector (SPD-M20A Photo Diode Array), and a Thermo Scientific Hypersil GOLD HPLC column (5 μm particle size, 4.6 × 50 mm)) and thin-layer chromatography (TLC) on EMD Millipore silica gel plates (glass backed, extra hard layer, 60 Å, 250 μm thickness, F254 indicator). Visualization of the developed plates was performed under UV-light (254 nm) irradiation, and subsequent gentle heating with $KMnO_4$, *p*-anisaldehyde, or ceric ammonium molybdate stains. Purification and isolation of products were performed via silica gel chromatography (both column and preparative thin-layer chromatography). Flash column chromatography was performed with either glass columns using Fisherbrand silica gel (40−63 μm particle size) or with a Yamazen Smart S4 Flash EPCLC W-Prep 2XY (dual channel) automated flash chromatography system on prefilled, premium, universal columns using ACS grade solvents. Organic solutions were concentrated under reduced pressure on a Heidolph temperature-controlled rotary evaporator equipped with a dry ice/isopropanol condenser or a Büchi temperature-controlled rotary evaporator equipped with an Ecodyst Ecochyll system.

3. Analytical Instrumentation. NMR spectral data were obtained using deuterated solvents obtained from Cambridge Isotope Laboratories, Inc. ^{1}H NMR and ^{13}C NMR data were recorded on Bruker AVB-400, AVQ-400, AV-500, DRX-500, AV-600, or AV-700 MHz spectrometers using $CDCl_3$, CD_3OD, or C_6D_6, typically at 20−23 °C. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR in $CDCl_3$).[24] Data for ^{1}H NMR spectroscopy are reported as follows; chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, bs = broad singlet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, ddd = doublet of doublets of doublets, dtd = doublet of triplets of doublets, dtt = doublet of triplets of triplets, ddq = doublet of doublets of quartets, dddd = doublet of doublets of doublets of doublets, td = triplet of doublets, tt = triplet of triplets, tdd = triplet of doublets of doublets, qd = quartet of doublets, qt = quartet of triplets), coupling constant (Hz), integration. Data for ^{13}C NMR spectroscopy are reported in terms of chemical shift (δ ppm). IR spectroscopic data were recorded on a Bruker ALPHA FT-IR spectrophotometer using a diamond attenuated total reflectance (ATR) accessory. Samples are loaded onto the diamond surface either neat or as a solution in organic solvent and the data acquired after the solvent had evaporated. Mass spectral data were obtained from the Mass Spectral Facility at the University of California, Berkeley, on a Finnigan/Thermo LTQ-FT instrument (ESI), or from the Catalysis Facility of Lawrence Berkeley National Laboratory (supported by US Department of Energy under contract no. DE-AC02-05CH11231), on a PerkinElmer AxION 2 UHPLC-TOF system (ESI or APCI). Data acquisition and processing were performed using the Xcalibur software. X-ray data were collected on a Bruker APEX-II CCD diffractometer with Mo Kα radiation (λ = 0.71073 Å) or a MicroStar-H X8 APEX-II diffractometer with Cu Kα radiation (λ = 1.54178 Å) (University of California, Berkeley; Supported by an NIH Shared Instrumentation Grant S10- RR027172). CYLview and ORTEP3 were used for graphic rendering.[25,26]

Synthesis of Aryl Bromides for Conjugate Additions in Table 1. *1-Bromo-4-(methoxymethoxy)benzene (**S1**).* 4-Bromophenol (25.2 g, 145 mmol, 1.0 equiv) and K_2CO_3 (30.2 g, 218 mmol, 1.5 equiv) were dissolved in acetone (200 mL, 0.67 M) at room temperature. To this stirring suspension was added MOMCl (16.5 mL, 218 mmol, 1.5 equiv) dropwise over 5 min. The reaction mixture was then heated in an oil bath at 60 °C for 20 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo to remove acetone. The resultant wet solid was dissolved in water (75 mL), then extracted with Et_2O (3 × 75 mL). The combined organic extracts were washed with brine (25 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography eluting with 0−10% EtOAc in hexanes gave **S1** as a colorless oil (26.3 g, 121 mmol, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 2H), 6.92 (m, 2H), 5.15 (s, 2H), 3.47 (s, 3H). Spectroscopic data for this compound were identical to those previously reported.[27]

*1-Bromo-3-(methoxymethoxy)benzene (**S2**).* 3-Bromophenol (1.37 g, 8.00 mmol, 1.0 equiv) and K_2CO_3 (1.66 g, 12.0 mmol, 1.5 equiv) were dissolved in acetone (12.0 mL, 0.67 M) at room temperature. To this stirring suspension was added MOMCl (0.91 mL, 12.0 mmol, 1.5 equiv) dropwise over 5 min. The reaction mixture was then heated in an oil bath at 60 °C for 16 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo to remove acetone. The resultant wet solid was dissolved in water (10 mL), then extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography eluting with 0−7% EtOAc in hexanes gave **S2** as a colorless oil (879 mg, 4.05 mmol, 51%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.22 (t, J = 1.7 Hz, 1H), 7.18−7.08 (m, 2H), 6.97 (dt, J = 6.6, 2.5 Hz, 1H), 5.16 (s, 2H), 3.47 (s, 3H). Spectroscopic data for this compound were identical to those previously reported.[28]

*1-Bromo-2-(methoxymethoxy)benzene (**S3**).* 2-Bromophenol (1.38 g, 8.00 mmol, 1.0 equiv) and K_2CO_3 (1.67 g, 12.0 mmol, 1.5 equiv) were dissolved in acetone (12.0 mL, 0.67 M) at room temperature. To this stirring suspension was added MOMCl (0.91 mL, 12.0 mmol, 1.5 equiv) dropwise over 5 min. The reaction mixture was then heated in an oil bath at 60 °C for 16 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo to remove acetone. The resultant wet solid was dissolved in water (10 mL), then extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography eluting with 0−7% EtOAc in hexanes gave **S3** as a colorless oil (1.13 g, 5.21 mmol, 65%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (dd, J = 7.9, 1.6 Hz, 1H), 7.25 (td, J = 7.6, 1.6 Hz, 1H), 7.15 (dd, J = 8.3, 1.5 Hz, 1H), 6.89 (td, J = 7.6, 1.5 Hz, 1H), 5.25 (s, 2H), 3.53 (s, 3H). Spectroscopic data for this compound were identical to those previously reported.[29]

*1,3-Dibromo-5-(methoxymethoxy)benzene (**S4**).* 3,5-Dibromophenol (1.37 g, 5.44 mmol, 1.0 equiv) and K_2CO_3 (1.18 g, 8.16 mmol, 1.5 equiv) were dissolved in acetone (8.0 mL, 0.67 M)

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at room temperature. To this stirring suspension was added MOMCl (0.41 mL, 8.16 mmol, 1.5 equiv) dropwise over 5 min. The reaction mixture was then heated in an oil bath at 60 °C for 16 h. The reaction mixture was then cooled to room temperature and concentrated in vacuo to remove acetone. The resultant wet solid was dissolved in water (5 mL), then extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with brine (5 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by column chromatography eluting with 0−7% EtOAc in hexanes gave **S4** as a colorless oil (1.17 g, 3.95 mmol, 73%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (t, J = 1.6 Hz, 1H), 7.15 (d, J = 1.6 Hz, 2H), 5.14 (s, 2H), 3.47 (s, 3H). Spectroscopic data for this compound were identical to those previously reported.[30]

General Procedure for Copper Conjugate Additions Using Aryl Bromides (Method 1). Aryl bromide (0.527 mmol, 4.0 equiv) and magnesium (14.0 mg, 0.580 mmol, 4.4 equiv) were dissolved in THF (1 mL, 0.53 M with respect to aryl bromide) and heated in an oil bath at 50 °C for 45 min or until the magnesium turnings had mostly dissolved. The reaction mixture was then allowed to cool to room temperature and then placed in an ice/water bath. The solution was then transferred via syringe to a chilled vial containing copper(I) iodide (50.0 mg, 0.263 mmol, 2.0 equiv) and stirred vigorously in the ice bath for 25 min. At this point, vinyl nitrile **9** (50.0 mg, 0.132 mmol, 1.0 equiv) was added as a solution in THF (0.5 mL, 0.26 M). The reaction mixture was removed from the ice bath, sealed with a Teflon cap, and heated in an oil bath at 45 °C and held at this temperature for 20 h. The reaction mixture was then allowed to cool to room temperature, quenched with MeOH (0.25 mL), diluted with NH_4Cl (saturated aqueous, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (3 × 2 mL), dried over Na_2SO_4, and concentrated in vacuo.

General Procedure for Copper Conjugate Additions Using Commercial Grignard Reagents (Method 2). Commercial Grignard solution (0.527 mmol, 4.0 equiv) was diluted to 0.53 M in THF in a sealed 1 dram vial under N_2 and cooled in an ice/water bath. The solution was then transferred via syringe to a chilled vial containing copper(I) iodide (50.0 mg, 0.263 mmol, 2.0 equiv) and stirred vigorously in the ice bath for 25 min. At this point, vinyl nitrile **9** (50.0 mg, 0.132 mmol, 1.0 equiv) was added as a solution in THF (0.5 mL, 0.26 M). The reaction mixture was removed from the ice bath, sealed with a Teflon cap, and heated in an oil bath at 45 °C for 20 h. The reaction mixture was then allowed to cool to room temperature, quenched with MeOH (0.25 mL), diluted with NH_4Cl (saturated aqueous, 5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed with brine (3 × 2 mL), dried over Na_2SO_4, and concentrated in vacuo.

*2-Methoxy-3-OMOM Tricycle (**10a**).* Prepared according to method 1. Purification by column chromatography (eluting with 60−100% CH_2Cl_2/hexanes, then 1−5% Et_2O/CH_2Cl_2) provided α-**10a** (trace amounts) as a colorless oil in <5% yield. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.03 (dd, J = 8.1, 1.2 Hz, 1H), 6.97 (t, J = 7.9 Hz, 1H), 6.88 (dd, J = 7.7, 1.1 Hz, 1H), 5.23−5.18 (m, 2H), 4.04 (ddd, J = 11.6, 8.7, 2.9 Hz, 1H), 3.98 (s, 1 H), 3.94 (s, 3H), 3.74 (s, 3H), 3.52 (s, 3H), 3.44 (s, 3H), 3.40 (dd, J = 7.4, 2.3 Hz, 2H), 3.25 (d, J = 8.4 Hz, 1H), 3.11 (ddd, J = 13.3, 9.0, 4.9 Hz, 1H), 2.40 (q, J = 12.5 Hz, 1H), 2.09 (ddd, J = 13.8, 4.9, 2.2 Hz, 1H), 2.00 (dtt, J = 11.8, 7.4, 4.5 Hz, 1H), 1.63 (ddd, J = 12.3, 9.1, 3.0 Hz, 1H), 1.47−1.32 (m, 3H), 0.88 (s, 9H), 0.02 (s, 3H), −0.01 (s, 3H). Spectroscopic data for this compound were identical to those previously reported.[15]

*3,5-Dimethoxy Tricycle (**10b**).* Prepared according to method 1. Run with modified equivalents of reagents (6.0 equiv of Grignard solution, 5.0 equiv of CuI). Purification by column chromatography (eluting with 60−100% CH_2Cl_2/hexanes, then 1−5% Et_2O/CH_2Cl_2) provided α-**10b** and β-**10b** in 76% combined yield.

α-**10b**. Isolated as a colorless oil (37.1 mg, 0.0717 mmol, 58%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.42 (d, J = 2.2 Hz, 2H), 6.33 (t, J = 2.2 Hz, 1H), 3.97 (bs, 1H), 3.79 (s, 6H), 3.73 (s, 3H), 3.68 (ddd, J = 11.4, 8.4, 2.8 Hz, 1H), 3.43 (s, 3H), 3.42 (s, 1H), 3.41 (s, 1H), 3.08 (d, J = 8.4 Hz, 1H), 3.00 (ddd, J = 13.6, 8.9, 4.8 Hz, 1H), 2.41 (q, J = 12.6 Hz, 1H), 2.12−2.06 (m, 1H), 2.02−1.95 (m, 1H), 1.74 (ddd, J = 12.4, 9.0, 2.9 Hz, 1H), 1.50−1.27 (m, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H). Spectroscopic data for this compound were identical to those previously reported.[15]

β-**10b**. Isolated as a pale yellow oil (11.6 mg, 0.0224 mmol, 18%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.43 (d, J = 2.2 Hz, 2H), 6.34 (t, J = 2.2 Hz, 1H), 3.92 (s, 1H), 3.82−3.77 (m, 1H), 3.78 (s, 6H), 3.78 (s, 3H), 3.64 (d, J = 9.7 Hz, 1H), 3.49 (dd, J = 9.8, 7.4 Hz, 1H), 3.43 (dd, J = 9.9, 7.3 Hz, 1H), 3.37 (s, 3H), 3.22 (ddd, J = 13.6, 8.9, 5.3 Hz, 1H), 2.28 (td, J = 13.0, 11.5 Hz, 1H), 2.15 (tdd, J = 12.0, 7.3, 4.7 Hz, 1H), 2.07 (dq, J = 14.4, 3.0 Hz, 1H), 1.86 (ddd, J = 12.5, 9.0, 3.1 Hz, 1H), 1.41−1.34 (m, 1H), 1.31 (qd, J = 13.1, 2.9 Hz, 1H), 1.19 (dddd, J = 14.9, 13.3, 3.7, 1.8 Hz, 1H), 0.90 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.7, 160.9, 145.0, 119.2, 106.7, 99.1, 79.6, 66.6, 63.1, 57.3, 55.4, 53.0, 46.1, 44.8, 41.4, 38.1, 32.3, 26.1, 25.4, 18.4, 16.4, −5.2; IR (thin film) 2950, 2930, 2900, 2856, 2237, 1738, 1596, 1460, 1250, 1205, 1153, 1105, 1085, 835, 775 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calc'd for $C_{28}H_{43}O_6NNaSi$ 540.2752; found 540.2743.

*2,5-Dimethoxy Tricycle (**10c**).* Prepared according to method 1. Purification by column chromatography (eluting with 60−100% CH_2Cl_2/hexanes, then 1−5% Et_2O/CH_2Cl_2) provided α-**10c** and β-**10c** in 93% combined yield.

α-**10c**. Isolated as a colorless oil (44.3 mg, 0.0856 mmol, 28%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.78 (d, J = 8.8 Hz, 1H), 6.77 (d, J = 3.0 Hz, 1H), 6.73 (dd, J = 8.8, 3.0 Hz, 1H), 3.97 (q, J = 1.8 Hz, 1H), 3.87 (ddd, J = 11.9, 8.7, 3.2 Hz, 1H), 3.79 (s, 3H), 3.76 (s, 3H), 3.74 (s, 3H), 3.44 (s, 3H), 3.42 (d, J = 8.7 Hz, 1H), 3.41−3.38 (m, 2H), 3.16 (ddd, J = 13.3, 9.1, 4.9 Hz, 1H), 2.31 (q, J = 12.3 Hz, 1H), 2.09 (dq, J = 14.0, 3.0 Hz, 1H), 1.96 (tt, J = 11.5, 3.8 Hz, 1H), 1.71 (ddd, J = 12.4, 9.1, 3.3 Hz, 1H), 1.47−1.32 (m, 3H), 0.88 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.6, 153.7, 151.5, 133.5, 120.6, 116.0, 112.2, 111.9, 77.2, 66.6, 60.6, 57.0, 55.9, 55.9, 52.8, 46.1, 44.0, 42.7, 38.4, 32.1, 26.1, 25.0, 18.4, 16.8, −5.3; IR (thin film) 2950, 2931, 2896, 2856, 2237, 1728, 1501, 1248, 1223, 1101, 1080, 1048, 835, 775 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calc'd for $C_{28}H_{43}O_6NNaSi$ 540.2752, found 540.2749.

β-**10c**. Isolated as a colorless oil (19.3 mg, 0.0372 mmol, 65%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.87 (d, J = 3.0 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H), 6.74 (dd, J = 8.8, 2.9 Hz, 1H), 4.12 (ddd, J = 11.4, 9.9, 2.9 Hz, 1H), 3.91 (p, J = 1.5 Hz, 1H), 3.80 (s, 3H), 3.79−3.75 (m, 1H), 3.76 (s, 3H), 3.75 (s, 3H), 3.54 (dd, J = 9.9, 7.0 Hz, 1H), 3.45 (dd, J = 9.9, 7.5 Hz, 1H), 3.39 (s, 3H), 3.17 (ddd, J = 13.5, 8.4, 4.9 Hz, 1H), 2.21 (td, J = 13.1, 11.2 Hz, 1H), 2.12 (tdd, J = 12.0, 7.3, 4.8 Hz, 1H), 2.07 (dq, J = 14.7, 3.3 Hz, 1H), 1.93 (ddd, J = 12.3, 8.7, 3.1 Hz, 1H), 1.42−1.29 (m, 2H), 1.19 (tdd, J = 14.7, 4.2, 2.0 Hz, 1H), 0.91 (s, 9H), 0.07 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.9, 153.7, 151.8, 131.9, 119.4, 115.0, 111.9, 111.2, 79.8, 66.8, 62.9, 57.5, 56.0, 55.9, 52.9, 43.8, 41.1, 39.4, 38.2, 29.7, 26.1, 25.6, 18.5, 16.6, −5.2; IR (thin film) 2952, 2928, 2855, 2234, 1739, 1591, 1496, 1250, 1219, 1106, 1087, 1054, 837, 776 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calc'd for $C_{28}H_{43}O_6NNaSi$ 540.2752, found 540.2747.

*4-OMOM Tricycle (**10d**).* Prepared according to method 1. Purification by column chromatography (eluting with 60−100% CH_2Cl_2/hexanes, then 1−5% Et_2O/CH_2Cl_2) provided α-**10d** and β-**10d** in 90% combined yield from 1.23 g (3.24 mmol) of nitrile **9**.

α-**10d**. Isolated as a colorless oil (1.10 g, 2.13 mmol, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20−7.17 (m, 2H), 7.00−6.96 (m, 2H), 5.21−4.93 (m, 2H), 3.97 (bs, 1H), 3.73 (s, 3H), 3.70 (ddd, J = 11.4, 8.3, 2.7 Hz, 1H), 3.47 (s, 3H), 3.45−3.37 (m, 2H), 3.43 (s, 3H), 3.03 (ddd, J = 13.5, 9.1, 4.5 Hz, 1H), 3.02 (d, J = 8.4 Hz, 1H), 2.43 (td, J = 13.1, 11.5 Hz, 1H), 2.09 (dq, J = 12.9, 2.7 Hz, 1H), 2.00 (dtd, J = 10.7, 6.2, 3.5 Hz, 1H), 1.72 (ddd, J = 12.4, 9.0, 2.9 Hz, 1H), 1.47−1.32 (m, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 156.2, 139.1, 128.0, 120.1, 116.8, 94.6, 77.1, 66.2, 60.4, 57.1, 56.1, 52.9, 48.7, 47.8, 43.4, 38.2, 33.1, 26.0, 24.8, 18.4, 16.6, −5.26, −5.29; IR (thin film) 2951, 2929, 2897, 2856, 2240, 1731, 1511, 1462, 1237, 1079, 1005, 815, 776 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calc'd for $C_{28}H_{43}O_6NNaSi$ 540.2752, found 540.2757.

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β-**10d**. Isolated as a colorless oil, which slowly solidified overnight at rt (394 mg, 0.761 mmol, 24%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 5.16 (qd, J = 6.8, 1.2 Hz, 2H), 3.92 (bs, 1H), 3.83−3.76 (m, 1H), 3.78 (s, 3H), 3.64 (d, J = 9.7 Hz, 1H), 3.49−3.41 (m, 2H), 3.74 (s, 3H) 3.37 (s, 3H), 3.25 (ddd, J = 13.6, 8.8, 5.4 Hz, 1H), 2.32 (q, J = 12.8 Hz, 1H), 2.15 (qd, J = 12.1, 6.7 Hz, 1H), 2.07 (dt, J = 14.6, 3.4 Hz, 1H), 1.82 (ddd, J = 12.4, 8.8, 2.8 Hz, 1H), 1.39−1.16 (m, 3H), 0.91 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.8, 156.4, 136.4, 129.5, 119.3, 116.3, 94.6, 79.6, 66.5, 63.1, 57.3, 56.1, 53.0, 45.1, 44.9, 41.4, 38.0, 32.9, 26.1, 25.4, 18.4, 16.4, −5.22, −5.24; IR (thin film) 2951, 2929, 2856, 2233, 1739, 1512, 1462, 1248, 1153, 1103, 1006, 836, 776 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calc'd for $C_{28}H_{43}O_6NNaSi$ 540.2752, found 540.2756.

*α-**10d** from β-**10d***. *β*-**10d** (366.9 mg, 0.709 mmol, 1.0 equiv) and K_2CO_3 (147.0 mg, 1.06 mmol, 1.5 equiv) were dissolved in MeOH (7.0 mL, 0.1 M) and heated in an oil bath at 80 °C for 1 h. The reaction mixture was allowed to cool to room temperature, at which time it was quenched with NH_4Cl (saturated aqueous, 5 mL), concentrated in vacuo to remove MeOH, and then extracted with CH_2Cl_2 (3 × 4 mL). The combined organic extracts were washed with brine (2 mL), dried over Na_2SO_4, and concentrated in vacuo to give a yellow oil. Purification by column chromatography (eluting with 5−35% EtOAc/hexanes) provided *α*-**10d** as a colorless oil (321.2 mg, 0.620 mmol, 88%).

*4-Methoxy Tricycle (**10e**)*. Prepared according to method 2. Run with modified equivalents of reagents (6.0 equiv of Grignard solution, 5.0 equiv of CuI). Purification by column chromatography (eluting with 60−100% CH_2Cl_2/hexanes, then 1−5% Et_2O/CH_2Cl_2) provided *α*-**10e** and *β*-**10e** in 88% combined yield.

α-**10e**. Isolated as a colorless oil (37.7 mg, 0.0773 mmol, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.6 Hz, 2H), 4.00 (bs, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.72 (ddd, J = 11.3, 8.4, 2.9 Hz, 1H), 3.46 (s, 3H), 3.49−3.39 (m, 2H), 3.07 (ddd, J = 13.3, 8.7, 4.8 Hz, 1H), 3.05 (d, J = 8.4 Hz, 1H), 2.47 (td, J = 12.9, 11.7 Hz, 1H), 2.12 (dq, J = 12.7, 2.6 Hz, 1H), 2.03 (qd, J = 7.2, 2.7 Hz, 1H), 1.75 (ddd, J = 12.2, 8.9, 2.9 Hz, 1H), 1.52−1.31 (m, 3H), 0.93 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 158.5, 137.8, 127.9, 120.1, 114.3, 77.0, 66.1, 57.0, 55.4, 52.8, 48.6, 47.8, 43.3, 38.1, 33.1, 26.0, 24.8, 18.3, 16.5, −5.3, −5.4; IR (thin film) 2948, 2928, 2855, 2238, 1736, 1612, 1514, 1435, 1250, 1106, 1077, 834, 809, 778 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calc'd for $C_{27}H_{41}O_5NNaSi$ 510.2646, found 510.2648.

β-**10e**. Isolated as a pale yellow oil (18.7 mg, 0.0383 mmol, 29%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23−7.13 (m, 2H), 6.92−6.67 (m, 2H), 3.91 (bs, 1H), 3.83−3.75 (m, 1H), 3.79 (s, 3H), 3.78 (s, 3H), 3.64 (d, J = 9.7 Hz, 1H), 3.46 (d, J = 7.4 Hz, 2H), 3.37 (s, 3H), 3.26 (ddd, J = 13.6, 8.8, 4.9 Hz, 1H), 2.33 (td, J = 13.1, 11.0 Hz, 1H), 2.15 (tdd, J = 12.3, 7.4, 4.9 Hz, 1H), 2.07 (dq, J = 14.9, 3.4 Hz, 1H), 1.82 (ddd, J = 12.3, 8.8, 3.0 Hz, 1H), 1.38−1.24 (m, 2H), 1.19 (dddd, J = 14.4, 12.2, 4.8, 2.0 Hz, 1H), 0.92 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.8, 158.6, 135.1, 129.4, 119.4, 114.0, 79.6, 66.5, 63.1, 57.3, 55.3, 53.0, 45.03, 44.98, 41.4, 38.0, 32.9, 26.1, 25.4, 18.4, 16.4, −5.22, −5.24; IR (thin film) 2950, 2930, 2899, 2856, 2234, 1738, 1612, 1514, 1462, 1249, 1179, 1102, 1085, 835, 775 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calc'd for $C_{27}H_{41}O_5NNaSi$ 510.2646, found 510.2645.

*2,4-Dimethoxy Tricycle (**10f**)*. Prepared according to method 1. Purification by column chromatography (eluting with 60−100% CH_2Cl_2/hexanes, then 1−5% Et_2O/CH_2Cl_2) provided *α*-**10f** and *β*-**10f** in 82% combined yield.

α-**10f**. Isolated as a colorless oil (35.3 mg, 0.0682 mmol, 52%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.08 (d, J = 8.3 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 6.40 (dd, J = 8.3, 2.4 Hz, 1H), 3.97 (bs, 1H), 3.84 (td, J = 8.6, 4.3 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H), 3.73 (s, 3H), 3.43 (s, 3H), 3.40 (d, J = 7.4 Hz, 2H), 3.35 (d, J = 8.5 Hz, 1H), 3.16 (ddd, J = 13.3, 9.0, 5.0 Hz, 1H), 2.29 (q, J = 12.3 Hz, 1H), 2.08 (ddd, J = 12.4, 5.2, 2.2 Hz, 1H), 1.96 (tdd, J = 11.7, 7.5, 4.7 Hz, 1H), 1.70 (ddd, J = 12.3, 9.0, 3.2 Hz, 1H), 1.46−1.28 (m, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.7, 160.1, 158.2, 129.8, 124.9, 120.8, 104.1, 99.2, 77.3, 66.5, 60.5, 57.0, 55.5, 55.3, 52.7, 45.6, 44.2, 42.6, 38.4, 31.9, 26.1, 25.0, 18.4, 16.8, −5.3; IR (thin film) 2950, 2930, 2892, 2856, 2237, 1730, 1613, 1507, 1463, 1257, 1209, 1102, 1083, 1038, 836, 776 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calc'd for $C_{28}H_{43}O_6NNaSi$ 540.2752, found 540.2762.

β-**10f**. Isolated as a colorless oil (20.7 mg, 0.0400 mmol, 30%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.20 (d, J = 8.3 Hz, 1H), 6.46 (dd, J = 8.3, 2.4 Hz, 1H), 6.44 (d, J = 2.4 Hz, 1H), 4.05 (ddd, J = 11.8, 9.8, 2.8 Hz, 1H), 3.90 (p, J = 1.4 Hz, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.74 (d, J = 9.8 Hz, 1H), 3.53−3.44 (m, 2H), 3.38 (s, 3H), 3.21 (ddd, J = 13.5, 8.4, 5.6 Hz, 1H), 2.22 (td, J = 13.1, 11.1 Hz, 1H), 2.12 (ddd, J = 14.4, 7.1, 1.9 Hz, 1H), 2.06 (dq, J = 14.5, 3.2 Hz, 1H), 1.93 (ddd, J = 12.8, 8.5, 2.8 Hz, 1H), 1.36−1.31 (m, 2H), 1.18 (dtd, J = 16.9, 6.0, 1.9 Hz, 1H), 0.93 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.0, 159.9, 158.4, 128.2, 123.3, 119.7, 104.2, 98.7, 79.8, 66.7, 62.8, 57.5, 55.5, 55.4, 52.9, 43.9, 41.1, 38.5, 38.1, 29.9, 26.1, 25.6, 18.5, 16.6, −5.2; IR (thin film) 2952, 2933, 2904, 2856, 2238, 1739, 1613, 1587, 1464, 1290, 1252, 1103, 1085, 836, 776 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calc'd for $C_{28}H_{43}O_6NNaSi$ 540.2752, found 540.2748.

*3-OMOM Tricycle (**10g**)*. Prepared according to method 1. Purification by column chromatography (eluting with 60−100% CH_2Cl_2/hexanes, then 1−5% Et_2O/CH_2Cl_2) provided *α*-**10g** and *β*-**10g** in 98% combined yield.

α-**10g**. Isolated as a colorless oil (46.2 mg, 0.0892 mmol, 68%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25−7.21 (m, 1H), 6.92 (s, 2H), 6.91 (d, J = 2.1 Hz, 1H), 5.19 (d, J = 6.8 Hz, 1H), 5.15 (d, J = 6.8 Hz, 1H), 3.97 (p, J = 1.3 Hz, 1H), 3.74 (s, 3H), 3.71 (ddd, J = 11.4, 8.4, 2.9 Hz, 1H), 3.48 (s, 3H), 3.45−3.38 (m, 2H), 3.43 (s, 3H), 3.08 (d, J = 8.4 Hz, 1H), 3.03 (ddd, J = 13.6, 9.0, 4.9 Hz, 1H), 2.44 (td, J = 13.0, 11.5 Hz, 1H), 2.09 (dq, J = 13.8, 2.4 Hz, 1H), 2.00 (dtd, J = 16.1, 7.4, 4.9 Hz, 1H), 1.74 (ddd, J = 12.3, 9.0, 2.8 Hz, 1H), 1.49−1.30 (m, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3, 157.8, 147.3, 130.2, 120.2, 112.0, 115.5, 114.3, 94.6, 77.1, 66.2, 60.5, 57.1, 56.2, 52.9, 49.3, 47.4, 43.4, 38.2, 33.0, 26.0, 24.8, 18.3, 16.6, −5.27, −5.30; IR (thin film) 2953, 2929, 2897, 2855, 2240, 1731, 1584, 1462, 1452, 1249, 1150, 1078, 1020, 981, 834, 774 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calc'd for $C_{28}H_{43}O_6NNaSi$ 540.2752, found 540.2749.

β-**10g**. Isolated as a colorless oil (20.8 mg, 0.0402 mmol, 30%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25−7.21 (m, 1H), 6.95 (dt, J = 7.7, 1.2 Hz, 1H), 6.92 (ddd, J = 5.2, 2.7, 1.7 Hz, 2H), 5.17 (s, 2H), 3.92 (t, J = 2.5 Hz, 1H), 3.81 (ddd, J = 11.8, 9.9, 2.9 Hz, 1H), 3.78 (s, 3H), 3.66 (d, J = 9.7 Hz, 1H), 3.50−3.43 (m, 2H), 3.48 (s, 3H), 3.37 (s, 3H), 3.24 (ddd, J = 13.6, 9.1, 5.2 Hz, 1H), 2.31 (td, J = 13.1, 11.0 Hz, 1H), 2.15 (dtd, J = 12.0, 7.3, 3.7 Hz, 1H), 2.07 (dq, J = 14.5, 3.3 Hz, 1H), 1.86 (ddd, J = 12.4, 8.9, 3.0 Hz, 1H), 1.40−1.28 (m, 2H), 1.19 (dddd, J = 14.9, 13.1, 4.2, 2.0 Hz, 1H), 0.91 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.7, 157.4, 144.6, 129.7, 121.8, 119.1, 116.8, 114.8, 94.7, 79.6, 66.5, 63.1, 57.3, 56.1, 53.0, 45.8, 44.8, 41.5, 38.1, 32.5, 26.1, 25.4, 18.4, 16.4, −5.23, −5.24; IR (thin film) 2951, 2928, 2898, 2856, 2238, 1739, 1609, 1585, 1462, 1249, 1151, 1080, 1025, 1009, 835, 775, 729 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calc'd for $C_{28}H_{43}O_6NNaSi$ 540.2752, found 540.2752.

*3-Methoxy Tricycle (**10h**)*. Prepared according to method 2. Purification by column chromatography (eluting with 60−100% CH_2Cl_2/hexanes, then 1−5% Et_2O/CH_2Cl_2) provided *α*-**10h** and *β*-**10h** in 92% combined yield from 1.26 mmol of nitrile **9**.

α-**10h**. Isolated as a colorless oil (430 mg, 0.882 mmol, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (t, J = 7.9 Hz, 1H), 6.87 (dt, J = 7.6, 1.2 Hz, 1H), 6.81 (t, J = 2.1 Hz, 1H), 6.77 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 3.97 (bs, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.71 (ddd, J = 11.3, 8.4, 2.9 Hz, 1H), 3.43 (s, 3H), 3.47−3.37 (m, 2H), 3.08 (d, J = 8.3 Hz, 1H), 3.03 (ddd, J = 13.6, 8.9, 4.8 Hz, 1H), 2.44 (td, J = 13.1, 11.6 Hz, 1H), 2.09 (dq, J = 14.1, 3.1 Hz, 1H), 2.00 (dtd, J = 16.0, 7.5, 4.9 Hz, 1H), 1.76 (ddd, J = 12.3, 9.0, 2.8 Hz, 1H), 1.48−1.33 (m, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3, 160.1, 147.3, 130.1, 120.0,

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119.1, 113.0, 112.2, 77.1, 66.3, 60.5, 57.1, 55.4, 52.9, 49.4, 47.5, 43.4, 38.2, 33.0, 26.0, 24.8, 18.4, 16.6, −5.26, −5.28; IR (thin film) 2951, 2929, 2897, 2857, 2239, 1732, 1600, 1463, 1255, 1119, 1084, 1051, 837, 777 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calc'd for $C_{27}H_{41}O_5NNaSi$ 510.2646, found 510.2647.

β-**10h**. Isolated as a colorless oil (132 mg, 0.271 mmol, 22%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, J = 7.9 Hz, 1H), 6.88 (dt, J = 7.5, 1.2 Hz, 1H), 6.80 (t, J = 2.1 Hz, 1H), 6.78 (ddd, J = 8.2, 2.6, 0.9 Hz, 1H), 3.92 (bs, 1H), 3.85−3.78 (m, 1H), 3.80 (s, 3H), 3.78 (s, 3H), 3.66 (d, J = 9.8 Hz, 1H), 3.46 (qd, J = 9.9, 7.4 Hz, 2H), 3.37 (s, 3H), 3.25 (ddd, J = 13.6, 8.9, 5.0 Hz, 1H), 2.31 (td, J = 13.1, 11.0 Hz, 1H), 2.15 (tdd, J = 12.3, 7.6, 4.9 Hz, 1H), 2.08 (dq, J = 14.1, 2.9 Hz, 1H), 1.87 (ddd, J = 12.4, 8.8, 3.0 Hz, 1H), 1.39−1.35 (m, 1H), 1.31 (qd, J = 12.9, 3.0 Hz, 1H), 1.20 (dddd, J = 14.8, 12.8, 4.0, 2.0 Hz, 1H), 0.91 (s, 9H), 0.06 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.7, 159.7, 144.5, 129.6, 120.7, 119.2, 114.6, 112.4, 79.6, 66.6, 63.1, 57.3, 55.3, 53.0, 45.9, 44.8, 41.5, 38.1, 32.5, 26.1, 25.4, 18.4, 16.4, −5.2; IR (thin film) 2951, 2930, 2856, 2359, 1737, 1602, 1462, 1422, 1257, 1230, 1105, 1086, 1053, 837, 813, 803,778 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calc'd for $C_{27}H_{41}O_5NNaSi$ 510.2646, found 510.2639.

*3-Bromo-5-OMOM Tricycle (**10i**)*. Prepared according to method 1. Purification by column chromatography (eluting with 60−100% CH_2Cl_2/hexanes, then 1−5% Et_2O/CH_2Cl_2) provided **10i** (39.8 mg, 0.0667 mmol) as an inseparable mixture of diastereomers (2.3:1 *α*:*β*-**10i**) in 49% combined yield. IR (thin film) 2953, 2930, 2895, 2857, 2241, 1732, 1602, 1568, 1462, 1451, 1437, 1256, 1152, 1083, 1026, 1007, 838, 776 cm^{-1}; HRMS (APCI) m/z $[M + H]^+$ calc'd for $C_{28}H_{43}{}^{81}BrNO_6Si$ 598.2017, found 598.2020.

α-**10i**. ^1H NMR (600 MHz, $CDCl_3$) δ 7.10 (dd, J = 2.3, 1.7 Hz, 1H), 7.04 (t, J = 1.6 Hz, 1H), 6.85 (t, J = 1.9 Hz, 1H), 5.17 (d, J = 6.9 Hz, 1H), 5.12 (d, J = 6.9 Hz, 1H), 3.98−3.95 (m, 1H), 3.75 (s, 3H), 3.67 (ddd, J = 11.5, 8.5, 3.0 Hz, 1H), 3.47 (s, 3H), 3.47−3.44 (m, 1H), 3.42 (s, 3H), 3.40−3.33 (m, 1H), 3.04 (d, J = 8.5 Hz, 1H), 3.00 (ddd, J = 13.3, 8.9, 4.9 Hz, 1H), 2.48−2.37 (m, 1H), 2.09 (dq, J = 13.8, 3.0 Hz, 1H), 2.03−1.98 (m, 1H), 1.71 (ddd, J = 12.4, 9.0, 2.9 Hz, 1H), 1.48−1.41 (m, 1H), 1.34 (tt, J = 10.7, 3.5 Hz, 2H), 0.90 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 158.4, 148.8, 123.1, 120.2, 119.7, 117.8, 114.7, 94.6, 77.0, 66.1, 60.4, 57.1, 56.3, 53.0, 49.1, 47.2, 43.2, 38.1, 32.9, 26.1, 24.8, 18.4, 16.5, −5.25, −5.28.

β-**10i**. ^1H NMR (600 MHz, $CDCl_3$) δ 7.23 (tdd, J = 7.3, 2.0, 0.8 Hz, 1H), 6.92 (s, 1H), 6.91 (d, J = 2.4 Hz, 1H), 5.20 (d, J = 6.8 Hz, 1H), 5.15 (d, J = 6.8 Hz, 1H), 3.98−3.95 (m, 1H), 3.74 (s, 3H), 3.71 (ddd, J = 11.5, 8.6, 3.0 Hz, 1H), 3.48 (s, 3H), 3.47−3.44 (m, 1H), 3.43 (s, 3H), 3.40−3.33 (m, 1H), 3.08 (d, J = 8.3 Hz, 1H), 3.00 (ddd, J = 13.3, 8.9, 4.9 Hz, 1H), 2.48−2.37 (m, 1H), 2.09 (dq, J = 13.8, 3.0 Hz, 1H), 2.03−1.98 (m, 1H), 1.74 (ddd, J = 12.4, 9.0, 2.9 Hz, 1H), 1.48−1.41 (m, 1H), 1.37 (tt, J = 10.7, 3.5 Hz, 2H), 0.89 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3, 157.8, 147.4, 130.2, 123.4, 120.0, 115.5, 114.3, 94.6, 77.1, 66.2, 60.5, 57.1, 56.2, 52.9, 49.3, 47.4, 43.4, 38.2, 33.1, 26.0, 24.8, 18.4, 16.6, −5.26, −5.29.

*2-OMOM Tricycle (**10j**)*. Prepared according to method 1. Purification by column chromatography (eluting with 60−100% CH_2Cl_2/hexanes, then 1−5% Et_2O/CH_2Cl_2) provided *α*-**10j** and *β*-**10j** in 76% combined yield.

α-**10j**. Isolated as a colorless oil (36.3 mg, 0.0701 mmol, 53%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.22 (dd, J = 7.6, 1.7 Hz, 1H), 7.19 (ddd, J = 8.2, 7.3, 1.7 Hz, 1H), 7.11 (dd, J = 8.3, 1.2 Hz, 1H), 6.95 (td, J = 7.4, 1.2 Hz, 1H), 5.25 (d, J = 6.9 Hz, 1H), 5.23 (d, J = 6.9 Hz, 1H), 4.01 (ddd, J = 11.6, 8.6, 3.0 Hz, 1H), 3.99 (dd, J = 3.2, 1.6 Hz, 1H), 3.72 (s, 3H), 3.50 (s, 3H), 3.45 (s, 3H), 3.42 (d, J = 7.3 Hz, 2H), 3.30 (d, J = 8.4 Hz, 1H), 3.15 (ddd, J = 13.4, 8.8, 4.9 Hz, 1H), 2.38 (q, J = 12.4 Hz, 1H), 2.13−2.07 (m, 1H), 1.98 (dq, J = 12.1, 5.9 Hz, 1H), 1.76 (ddd, J = 12.2, 8.9, 3.0 Hz, 1H), 1.48−1.32 (m, 3H), 0.89 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.6, 155.0, 133.2, 128.8, 128.3, 122.1, 120.5, 114.2, 94.4, 77.2, 66.6, 60.6, 57.0, 56.3, 52.8, 44.79, 44.76, 43.0, 38.4, 32.0, 26.0, 25.0, 18.4, 16.8, −5.2, −5.3; IR (thin film) 2952, 2929, 2895, 2856, 2239, 1728, 1492, 1471, 1249, 1077, 1000, 835, 775, 753 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calc'd for $C_{28}H_{43}O_6NNaSi$ 540.2752, found 540.2748.

β-**10j**. Isolated as a colorless oil (15.5 mg, 0.0299 mmol, 23%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.33 (dd, J = 7.7, 1.6 Hz, 1H), 7.21 (ddd, J = 8.2, 7.4, 1.7 Hz, 1H), 7.10 (dd, J = 8.3, 1.2 Hz, 1H), 7.00 (td, J = 7.5, 1.2 Hz, 1H), 5.25 (d, J = 6.6 Hz, 1H), 5.20 (d, J = 6.6 Hz, 1H), 4.17 (td, J = 11.2, 2.7 Hz, 1H), 3.93 (p, J = 1.3 Hz, 1H), 3.78 (d, J = 9.8 Hz, 1H), 3.75 (s, 3H), 3.52 (s, 3H), 3.54−3.47 (m, 2H), 3.40 (s, 3H), 3.23 (ddd, J = 13.5, 8.5, 4.9 Hz, 1H), 2.26 (td, J = 13.2, 11.1 Hz, 1H), 2.18−2.09 (m, 1H), 2.08 (dq, J = 14.4, 3.1 Hz, 1H), 1.99 (ddd, J = 12.1, 8.4, 2.7 Hz, 1H), 1.39−1.30 (m, 2H), 1.20 (ddd, J = 17.1, 10.4, 4.3 Hz, 1H), 0.93 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.9, 155.4, 131.4, 128.4, 127.8, 122.0, 119.4, 114.0, 95.0, 79.8, 66.7, 62.9, 57.4, 56.3, 52.9, 43.7, 41.3, 38.9, 38.1, 29.9, 26.1, 25.5, 18.5, 16.6, −5.18, −5.20; IR (thin film) 2951, 2928, 2896, 2855, 2236, 1739, 1492, 1457, 1249, 1231, 1082, 1003, 836, 776, 754 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calc'd for $C_{28}H_{43}O_6NNaSi$ 540.2752, found 540.2746.

*2-Methoxy Tricycle (**10k**)*. Prepared according to method 2. Purification by column chromatography (eluting with 60−100% CH_2Cl_2/hexanes, then 1−5% Et_2O/CH_2Cl_2) provided *α*-**10k** and *β*-**10k** in 57% combined yield from 200 mg (0.527 mmol) of nitrile **9**.

α-**10k**. Isolated as a colorless oil (110. mg, 0.223 mmol, 42%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.22 (td, J = 7.6, 1.7 Hz, 1H), 7.19 (dd, J = 7.6, 1.6 Hz, 1H), 6.89 (td, J = 7.5, 1.0 Hz, 1H), 6.86 (d, J = 8.2 Hz, 1H), 3.97 (t, J = 2.1 Hz, 1H), 3.92 (ddd, J = 11.7, 8.5, 3.1 Hz, 1H), 3.84 (s, 3H), 3.73 (s, 3H), 3.44 (s, 3H), 3.41 (dd, J = 7.4, 1.3 Hz, 2H), 3.38 (d, J = 8.5 Hz, 1H), 3.18 (ddd, J = 13.3, 8.9, 4.9 Hz, 1H), 2.32 (q, J = 12.3 Hz, 1H), 2.09 (dq, J = 12.4, 2.5 Hz, 1H), 1.97 (dtt, J = 11.8, 7.6, 4.5 Hz, 1H), 1.75 (ddd, J = 12.3, 9.0, 3.2 Hz, 1H), 1.46−1.31 (m, 3H), 0.88 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.7, 157.3, 132.4, 129.3, 128.3, 120.8, 120.7, 111.0, 77.3, 66.5, 60.6, 57.0, 55.3, 52.8, 45.7, 44.1, 42.7, 38.3, 31.8, 26.0, 25.0, 18.4, 16.8, −5.2; IR (thin film) 2951, 2930, 2856, 2239, 1730, 1601, 1494, 1462, 1247, 1102, 1082, 837, 776, 753 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calc'd for $C_{27}H_{41}O_5NNaSi$ 510.2646, found 510.2653.

β-**10k**. Isolated as a colorless oil (37.7 mg, 0.0773 mmol, 15%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.31 (dd, J = 7.7, 1.6 Hz, 1H), 7.23 (ddd, J = 8.2, 7.4, 1.7 Hz, 1H), 6.95 (td, J = 7.5, 1.1 Hz, 1H), 6.87 (dd, J = 8.2, 1.1 Hz, 1H), 4.13 (ddd, J = 11.4, 9.7, 2.7 Hz, 1H), 3.92 (t, J = 2.9 Hz, 1H), 3.85 (s, 3H), 3.78 (d, J = 9.7 Hz, 1H), 3.75 (s, 3H), 3.54−3.46 (m, 2H), 3.40 (s, 3H), 3.23 (ddd, J = 13.5, 8.5, 4.9 Hz, 1H), 2.24 (td, J = 13.1, 11.0 Hz, 1H), 2.13 (dt, J = 14.0, 7.4 Hz, 1H), 2.07 (dq, J = 14.5, 3.3 Hz, 1H), 1.99 (ddd, J = 12.2, 8.5, 2.8 Hz, 1H), 1.37−1.30 (m, 2H), 1.23−1.15 (m, 1H), 0.93 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.8, 157.3, 130.6, 128.1, 127.5, 120.5, 119.3, 110.3, 79.6, 66.5, 62.6, 57.3, 55.3, 52.7, 43.5, 41.0, 38.8, 37.9, 29.5, 25.9, 25.4, 18.3, 16.4, −5.38, −5.39; IR (thin film) 2950, 2930, 2857, 2235, 1740, 1494, 1463, 1244, 1103, 1086, 1056, 1033, 837, 776, 752 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calc'd for $C_{27}H_{41}O_5NNaSi$ 510.2646, found 510.2641.

*2,6-Dimethoxy Tricycle (**10m**)*. Prepared according to method 1. Purification by column chromatography (eluting with 60−100% CH_2Cl_2/hexanes, then 1−5% Et_2O/CH_2Cl_2) provided *α*-**10m** as a single diastereomer (52.4 mg, 0.101 mmol, 83%). ^1H NMR (600 MHz, $CDCl_3$) δ 7.16 (t, J = 8.3 Hz, 1H), 6.54 (d, J = 8.3 Hz, 2H), 4.48 (ddd, J = 11.9, 10.2, 3.5 Hz, 1H), 3.90 (t, J = 2.5 Hz, 1H), 3.80 (s, 6H), 3.79 (s, 3H), 3.56−3.43 (m, 3H), 3.40 (s, 3H), 3.35 (dd, J = 9.9, 7.9 Hz, 1H), 2.14−1.98 (m, 3H), 1.91 (ddd, J = 12.2, 9.2, 3.5 Hz, 1H), 1.40 (dq, J = 11.6, 3.6 Hz, 1H), 1.32 (qd, J = 13.1, 3.0 Hz, 1H), 1.18 (tdd, J = 13.5, 3.8, 1.9 Hz, 1H), 0.89 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 158.9, 128.3, 120.30, 118.5, 104.3, 80.2, 67.2, 63.5, 57.5, 55.7, 52.8, 43.1, 40.9, 38.6, 34.8, 31.0, 26.1, 25.8, 18.5, 16.9, −5.17, −5.22; IR (thin film) 2951, 2931, 2895, 2856, 2237, 1739, 1594, 1474, 1594, 1474, 1249, 1102, 838, 775 cm^{-1}; HRMS (ESI) m/z $[M + Na]^+$ calc'd for $C_{28}H_{43}O_6NNaSi$ 540.2752, found 540.2746.

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Synthesis of Dienone 15 from Ester α-10d. *Alcohol Derived from Ester α-10d (S5).* Ester **α-10d** (1.732 g, 3.34 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (33 mL, 0.1 M) and cooled in an ice/water bath. Red-Al solution (3.4 mL, 11.7 mmol, 3.5 equiv, 70 wt % in PhMe) was added dropwise over 5 min. The reaction mixture was stirred in the bath for 1 h, then allowed to warm gradually to room temperature over 2.25 h. The reaction mixture was then diluted with THF (25 mL), at which point it was cooled in an ice/water bath again and quenched by the serial addition of H_2O (88 μL), NaOH (2.0 M aqueous, 88 μL), and H_2O (3 × 88 μL). The reaction mixture was allowed to warm gradually to room temperature over 12 h, then filtered over a plug of Celite, which was rinsed with THF (25 mL), then EtOAc (50 mL). The combined organic filtrates were concentrated in vacuo to give a colorless oil. Purification by column chromatography (eluting with 17−37% EtOAc/hexanes) provided alcohol **S5** as a clear gum (1.365 g, 2.79 mmol, 83%). ^{1}H NMR (700 MHz, C_6D_6) δ 7.21 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.05 (dd, *J* = 8.7, 1.0 Hz, 2H), 4.86 (qd, *J* = 6.9, 1.0 Hz, 2H), 3.80 (ddd, *J* = 11.4, 8.4, 2.7 Hz, 1H), 3.33 (dd, *J* = 14.8, 7.0 Hz, 1H), 3.32 (dd, *J* = 14.8, 7.0 Hz, 1H), 3.28 (s, 3H), 3.24 (d, *J* = 11.1 Hz, 1H), 3.20 (s, 1H), 3.15 (s, 3H), 3.06 (d, J = 8.5 Hz, 1H), 2.52 (ddd, *J* = 13.4, 8.6, 4.7 Hz, 1H), 2.39 (q, *J* = 12.4 Hz, 1H), 1.79−1.71 (m, 2H), 1.70 (dq, *J* = 14.8, 3.1 Hz, 1H), 1.63 (ddd, *J* = 12.2, 8.7, 2.7 Hz, 1H), 1.34 (qd, *J* = 13.4, 3.4 Hz, 1H), 1.22 (dd, *J* = 13.3, 3.5 Hz, 1H), 1.01 (tt, *J* = 12.9, 2.3 Hz, 1H), 0.97 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (176 MHz, C_6D_6) δ 156.7, 140.5, 128.3, 121.5, 117.0, 94.5, 78.0, 66.8, 63.5, 56.9, 55.8, 55.5, 48.2, 45.8, 39.7, 37.8, 34.3, 26.1, 24.3, 18.5, 17.4, −5.3; IR (thin film) 3474, 2952, 2929, 2890, 2857, 2234, 1511, 1250, 1088, 1007, 836, 776 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calc'd for $C_{27}H_{43}NNaO_5Si$ 512.2803, found 512.2806.

MOM Ether 12. Alcohol **S5** (2.60 g, 5.30 mmol, 1.0 equiv) was dissolved in PhMe (26 mL, 0.2 M) in a round-bottomed flask. DIPEA (3.70 mL, 21.2 mmol, 4.0 equiv) was added to the stirring mixture, followed by MOMCl (1.60 mL, 21.2 mmol, 4.0 equiv). The flask was fitted with a reflux condenser and heated in an oil bath at 70 °C for 12 h. The reaction mixture was then allowed to cool to room temperature, at which point it was quenched by the addition of $NaHCO_3$ (saturated aqueous, 20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to provide MOM ether **12** as an orange oil (2.84 g, 5.30 mmol, >99% crude yield), which was advanced without further purification. ^{1}H NMR (500 MHz, C_6D_6) δ 7.22 (d, *J* = 8.7 Hz, 2H), 7.05 (d, *J* = 8.7 Hz, 2H), 4.91−4.69 (m, 2H), 4.30 (bs, 2H), 3.83 (ddd, *J* = 11.4, 8.4, 2.7 Hz, 1H), 3.34−3.29 (m, 1H), 3.30 (s, 3H), 3.31−3.25 (m, 3H), 3.21 (d, *J* = 9.9 Hz, 1H), 3.13 (s, 3H), 3.12 (s, 1H), 3.10 (s, 3H), 2.57 (ddd, *J* = 13.4, 8.6, 4.8 Hz, 1H), 2.39 (q, *J* = 12.3 Hz, 1H), 1.76 (qt, *J* = 7.3, 3.6 Hz, 1H), 1.71−1.63 (m, 1H), 1.66 (t, *J* = 3.7 Hz, 1H), 1.33 (qd, *J* = 13.0, 2.4 Hz, 1H), 1.14 (dd, *J* = 13.4, 3.5 Hz, 1H), 1.08−0.97 (m, 1H), 0.95 (s, 9H), 0.01 (s, 3H), −0.01 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 156.7, 140.5, 128.2, 120.9, 117.0, 96.5, 94.4, 78.0, 68.9, 66.5, 57.0, 55.5, 55.1, 54.4, 48.3, 46.8, 40.6, 37.8, 34.0, 26.1, 24.2, 18.4, 17.3, −5.3; IR (thin film) 2950, 2929, 2889, 2856, 2235, 1732, 1610, 1511, 1151, 1080, 1039, 833, 774 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calc'd for $C_{29}H_{47}NNaO_6Si$ 556.3065, found 556.3077.

Amide 8. MOM ether **12** (1.34 g, 2.51 mmol, 1.0 equiv) and $Rh(PPh_3)_3Cl$ (234.5 mg, 0.251 mmol, 10 mol %) were dissolved in PhMe (5.0 mL, 0.5 M) in a round-bottomed flask. Acetaldoxime (3.8 mL, 62.8 mmol, 25 equiv) was sparged with N_2 for 15 min, then added to the flask, which was then fitted with a reflux condenser. The reaction mixture was heated to 120 °C and held at this temperature for 14 h, at which point it was allowed to cool to room temperature, mixed with silica (10 mL), and concentrated carefully in vacuo. This mixture was then loaded directly onto a column for purification. Purification by column chromatography (eluting with 1−70% EtOAc/hexanes) provided amide **8** as an amorphous white solid (974 mg, 1.77 mmol, 70% over 2 steps, 81% based on recovered **12**). ^{1}H NMR (500 MHz, C_6D_6) δ 7.40 (d, *J* = 8.6 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.15 (bs, 1H), 6.13 (s, 1H), 4.86 (s, 2H), 4.37 (d, *J* = 6.4 Hz, 1H), 4.32 (d, *J* = 6.5 Hz, 1H), 4.16 (ddd, *J* = 10.7, 8.0, 2.3 Hz, 1H), 3.89 (d, *J* = 9.5 Hz, 1H), 3.66 (t, *J* = 2.9 Hz, 1H), 3.44 (d, *J* = 9.6 Hz, 1H), 3.43−3.36 (m, 1H), 3.40 (t, *J* = 7.1 Hz, 1H), 3.19 (s, 3H), 3.18 (s, 1H), 3.13 (s, 3H), 3.09 (s, 3H), 2.62 (ddd, *J* = 13.0, 8.2, 4.8 Hz, 1H), 2.52 (q, *J* = 12.1 Hz, 1H), 1.91 (ddq, *J* = 15.8, 7.1, 4.1 Hz, 1H), 1.77 (dq, *J* = 14.1, 2.9 Hz, 1H), 1.66 (ddd, *J* = 11.6, 6.9, 2.4 Hz, 1H), 1.47 (qd, *J* = 13.1, 3.4 Hz, 1H), 1.27 (ddd, *J* = 12.8, 6.4, 2.8 Hz, 1H), 1.16 (tt, *J* = 13.5, 2.7 Hz, 1H), 0.98 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 174.8, 156.2, 143.6, 128.6, 117.0, 96.6, 94.5, 77.4, 71.6, 66.9, 61.4, 56.6, 55.5, 55.2, 53.5, 45.4, 42.3, 38.2, 34.0, 26.2, 24.3, 18.5, 17.8, −5.27, −5.29; IR (thin film) 3500−3300, 2950, 2930, 2889, 2821, 1673, 1510, 1153, 1089, 836, 776 cm^{-1}; HRMS (ESI) *m*/*z* [M + H]$^+$ calc'd for $C_{29}H_{50}NO_7Si$ 552.3351, found 552.3360.

Alcohol 13. Amide **8** (719 mg, 1.30 mmol, 1.0 equiv) was dissolved in MeCN (8.7 mL, 0.15 M) in a round-bottomed flask open to air. $PhI(OAc)_2$ (548 mg, 1.70 mmol, 1.3 equiv) was added and the reaction mixture was stirred vigorously for 5 min, at which point KOH (365 mg, 6.51 mmol, 5.0 equiv) was added as a solution in H_2O (4.3 mL, 0.30 M with respect to amide **8**). The reaction mixture was capped loosely and stirred at room temperature for 6 h. The resulting pink-orange solution was diluted with H_2O (5 mL) and concentrated in vacuo to remove the MeCN. The aqueous material was extracted with EtOAc (3 × 10 mL); then the combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Amine **S6** was obtained as a pink oil, which was then azeotropically dried with benzene (3 × 5 mL). Amine **S6** was advanced without further purification.

Amine **S6** (700 mg) was dissolved in CH_2Cl_2 (13 mL, 0.1 M), then cooled in an ice/water bath. Pyridine (0.53 mL, 6.58 mmol, 5.0 equiv) was added, followed by Ac_2O (0.37 mL, 3.91 mmol, 3.0 equiv). Each addition was performed dropwise over 5 min by syringe. The reaction mixture was allowed to warm gradually to room temperature over 16 h, at which time it was quenched with $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to give acetamide **S7** as an orange oil, which was advanced without further purification.

Acetamide **S7** (740 mg, 1.31 mmol, 1.0 equiv) was dissolved in THF (13 mL, 0.1 M) in a round-bottomed flask open to air. TBAF solution (2.6 mL, 2.62 mmol, 2.0 equiv, 1 M in THF) was added and the reaction mixture stirred for 15 h. The crude reaction mixture was concentrated in vacuo to give a brown oil. Purification by column chromatography (eluting with 5−55% acetone/CH_2Cl_2) provided alcohol **13** (445 mg, 0.985 mmol, 75% over 3 steps) as a white gum. ^{1}H NMR (500 MHz, C_6D_6, 343 K)* δ 7.33 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 5.42 (d, *J* = 10.1 Hz, 1H), 5.09 (t, *J* = 9.4 Hz, 1H), 4.88 (s, 2H), 4.76 (d, *J* = 6.5 Hz, 1H), 4.66 (d, *J* = 6.2 Hz, 1H), 3.42 (dd, *J* = 16.5, 10.0 Hz, 2H), 3.33 (s, 3H), 3.29 (d, *J* = 7.6 Hz, 1H), 3.24 (t, *J* = 8.5 Hz, 1H), 3.16 (s, 3H), 2.94 (bs, 1H), 2.91 (s, 3H), 2.69−2.57 (m, 1H), 2.33 (q, *J* = 12.6 Hz, 1H), 1.75 (d, *J* = 15.5 Hz, 1H), 1.62 (s, 3H), 1.56 (t, *J* = 10.7 Hz, 1H), 1.36−1.26 (m, 2H), 1.20 (t, *J* = 12.6 Hz, 1H), 1.06−0.95 (m, 1H); ^{13}C NMR (126 MHz, C_6D_6, 343 K) δ 168.2, 156.5, 140.9, 128.4, 117.1, 98.0, 95.0, 78.4, 70.4, 66.3, 62.6, 55.5, 55.4, 55.1, 52.5, 50.8, 38.7, 38.4, 33.0, 24.2, 23.2, 17.7; IR (thin film) 3375, 2932, 2889, 2824, 1651, 1509, 1232, 1150, 1044, 919, 830 cm^{-1}; HRMS (ESI) *m*/*z* [M + Na]$^+$ calc'd for $C_{24}H_{37}NNaO_7$ 474.2462, found 474.2451. *^{1}H NMR peaks did not fully coalesce at 343 K, so peaks are reported for major rotamer at that temperature.

Piperidine 14. Alcohol **13** (445 mg, 0.984 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (10. mL, 0.1 M). Et_3N (0.69 mL, 4.92 mmol, 5.0 equiv) was added via syringe, followed by MsCl (120 μL, 1.48 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 3.5 h, then quenched by the addition of brine (10 mL). The solution was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to give mesylate **S8** as a pale brown foam (530 mg), which was advanced without further purification.

Mesylate **S8** (530 mg, 0.984 mmol, 1.0 equiv) was dissolved in DMF (10. mL, 0.1 M). KH (59.2 mg, 1.48 mmol, 1.5 equiv) was

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added and the reaction mixture was heated in an oil bath at 50 °C for 15 h. At this point, conversion was judged to be incomplete (by TLC and LC−MS analysis) and additional KH (39.0 mg, 0.984 mmol, 1.0 equiv) was added after allowing the reaction mixture to cool to room temperature. The reaction mixture was returned to the oil bath and heated at 50 °C for 2 h. The reaction mixture was cooled to room temperature, diluted with brine (10 mL) and H_2O (90 mL), and extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to give a yellow oil. Purification by column chromatography (eluting with 45−70% acetone/CH_2Cl_2) provided piperidine **14** (366 mg, 0.844 mmol, 86% over 2 steps) as a white gum. ^{1}H NMR (500 MHz, C_6D_6, 343 K) δ 7.09−6.97 (m, 4H), 4.87 (d, J = 1.1 Hz, 2H), 4.54 (d, J = 14.3 Hz, 1H), 4.29 (s, 1H), 4.29−4.22 (m, 1H), 4.23 (s, 1H), 3.62 (dd, J = 10.2, 7.5 Hz, 1H), 3.36 (d, J = 9.7 Hz, 1H), 3.14 (dd, J = 17.0, 7.9 Hz, 1H), 3.14 (s, 3H), 3.08 (s, 3H), 3.05 (s, 3H), 3.02 (d, J = 9.7 Hz, 1H), 2.82 (dd, J = 14.5, 4.6 Hz, 1H), 2.27 (s, 3H), 2.26 (bs, 1H), 2.18 (dt, J = 13.2, 6.5 Hz, 1H), 1.84−1.78 (m, 1H), 1.73 (dd, J = 13.4, 9.8 Hz, 1H), 1.69−1.63 (m, 1H), 1.65−1.58 (m, 1H), 1.38 (t, J = 4.1 Hz, 1H), 1.26 (td, J = 14.1, 5.5 Hz, 1H); ^{13}C NMR (126 MHz, C_6D_6, 343 K) δ 167.2, 156.3, 137.5, 127.5, 116.9, 97.0, 95.0, 77.4, 66.5, 64.8, 56.6, 55.6, 55.1, 53.0, 47.5, 42.1, 41.1, 33.5, 33.0, 30.1, 24.3, 22.1; IR (thin film) 2923, 2897, 2863, 2818, 1631, 1511, 1422, 1016, 916, 513 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calc'd for $C_{24}H_{35}NNaO_6$ 456.2357, found 456.2346.

Aldehyde 7. Piperidine **14** (79.0 mg, 0.182 mmol, 1.0 equiv) was dissolved in THF (1.4 mL, 75 mM) in a round-bottomed flask left open to air. A 6 N HCl aqueous solution (0.84 mL, 5.0 mmol, 28 equiv) was added and the reaction mixture was stirred at room temperature for 28 h, at which point it was concentrated in vacuo to remove THF. The aqueous phase was diluted with brine (5 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo to give diol **S9** a white solid (52 mg, 0.151 mmol, 84% crude yield), which was advanced without further purification. IR (thin film) 3288, 2966, 2930, 2818, 1609, 1515, 1452, 1264, 1105, 830 cm^{-1}; HRMS (ESI) m/z [M + Na]$^+$ calc'd for $C_{20}H_{27}NNaO_4$ 368.1832, found 368.1825.

Diol **S9** (52.0 mg, 0.151 mmol, 1.0 equiv) was suspended in CH_2Cl_2 (4.0 mL, 37 mM). DMSO (75 μL, 1.05 mmol, 7.0 equiv) was added and the resulting suspension was cooled in a dry ice/acetone bath at −78 °C. Oxalyl chloride (26 μL, 0.303 mmol, 2.0 equiv) was added dropwise and the reaction mixture was maintained at −78 °C for 75 min. Et_3N (210 μL, 1.51 mmol, 10. equiv) was then added via syringe and the solution was maintained at −78 °C for 45 min. The light yellow solution was removed from the bath and stirred at room temperature for 1 h, at which point it was quenched with NH_4Cl (saturated aqueous, 15 mL) and brine (5 mL). Upon extraction with CH_2Cl_2 (3 × 5 mL), the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by column chromatography (eluting with 0−40% acetone/CH_2Cl_2) provided aldehyde 7 (30.0 mg, 0.0874 mmol, 58%) as a colorless oil. ^{1}H NMR (700 MHz, C_6D_6)* δ 9.37 (s, 1H), 7.00 (d, J = 8.1 Hz, 2H), 6.82 (d, J = 8.4 Hz, 2H),4.93 (bs, 1H), 4.32 (d, J = 14.3 Hz, 1H), 3.53 (dd, J = 10.3, 6.8 Hz, 1H), 3.42 (dd, J = 9.9, 6.1 Hz, 1H), 3.21 (d, J = 1.5 Hz, 3H), 3.06 (dd, J = 14.4, 5.3 Hz, 1H), 2.56 (t, J = 4.9 Hz, 1H), 2.33 (d, J = 1.4 Hz, 3H), 2.21 (dt, J = 13.1, 6.3 Hz, 1H), 2.03 (td, J = 6.5, 3.4 Hz, 1H), 1.98 (dd, J = 14.3, 9.6 Hz, 1H), 1.92−1.89 (m, 1H), 1.86 (q, J = 5.2 Hz, 1H), 1.56−1.50 (m, 1H), 1.47 (qd, J = 12.3, 4.9 Hz, 1H); ^{13}C NMR (176 MHz, C_6D_6) δ 206.9, 169.1, 154.9, 131.5, 128.8, 115.9, 80.4, 65.2, 62.2, 56.5, 47.6, 41.7, 41.4, 32.5, 30.8, 29.1, 24.1, 22.4; IR (thin film) 3252, 2958, 2934, 2856, 2358, 1717, 1613, 1591, 1514, 1450, 1260, 1090, 1027, 799 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calc'd for $C_{20}H_{26}NO_4$ 344.1856, found 344.1855. *Rotameric mixture (3:1 ratio of rotamers at 298 K); peaks reported for major rotamer.

Dienone 15. Aldehyde 7 (23.0 mg, 0.0670 mmol, 1.0 equiv) and $NaHCO_3$ (23.4 mg, 0.279 mmol, 4.0 equiv) were suspended in MeOH (3.0 mL, 22 mM), then sonicated until dissolution was nearly complete. The mixture was cooled in an ice/water bath at 0 °C before $PhI(OAc)_2$ (22.6 mg, 0.0702 mmol, 1.04 equiv) was added. The reaction mixture was allowed to warm gradually to room temperature over 3.5 h, at which point H_2O (0.5 mL) was added and the mixture concentrated in vacuo to remove MeOH. The resulting residue was diluted with H_2O (1.0 mL) and extracted with EtOAc (3 × 1 mL). The combined organic extracts were washed with brine (0.5 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by preparatory TLC (eluting with 20−50% acetone/CH_2Cl_2) provided dienone **15** (13.0 mg, 0.0348 mmol, 52%) as a colorless oil. ^{1}H NMR (600 MHz, C_6D_6)* δ 6.62 (dd, J = 10.4, 3.2 Hz, 1H), 6.56 (dd, J = 10.4, 3.2 Hz, 1H), 6.03 (dd, J = 10.4, 2.0 Hz, 1H), 5.98 (dd, J = 10.4, 2.0 Hz, 1H), 4.90 (s, 1H), 4.21 (d, J = 14.4 Hz, 1H), 4.16 (s, 1H), 3.27 (dd, J = 10.9, 7.0 Hz, 1H), 3.21 (s, 3H), 3.00 (s, 3H), 2.68 (dd, J = 13.7, 6.2 Hz, 1H), 2.14 (dd, J = 7.2, 4.7 Hz, 1H), 2.01 (s, 3H), 2.00−1.95 (m, 1H), 1.68−1.61 (m, 1H), 1.50 (dq, J = 13.3, 2.9 Hz, 1H), 1.40−1.33 (m, 2H), 1.23 (dt, J = 7.5, 3.3 Hz, 1H), 1.10 (t, J = 8.5 Hz, 2H); ^{13}C NMR (126 MHz, C_6D_6) δ 183.7, 168.2, 148.9, 147.6, 128.6, 128.5, 103.8, 78.4, 74.9, 58.1, 56.8, 56.3, 52.5, 48.9, 41.3, 37.6, 32.5, 29.6, 29.4, 24.1, 22.4; IR (thin film) 2932, 2828, 1720, 1671, 1629, 1450, 1378, 1251, 1194, 1135, 1090, 948 cm^{-1}; HRMS (ESI) m/z [M + H]$^+$ calc'd for $C_{21}H_{28}NO_5$ 374.1962, found 374.1942. *Rotameric mixture (4:1 ratio of rotamers at 298 K); peaks reported for major rotamer.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b01967.

^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

X-ray crystallographic data for compound β-**10d** (CCDC 1859315) (CIF)

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Notes

The authors declare no competing financial interest.

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