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Regiochemistry Discoveries in the Use of Isoxazole as a Handle for the Rapid Construction of an All-Carbon Macrocyclic Precursor in the Synthetic Studies of Celastrol

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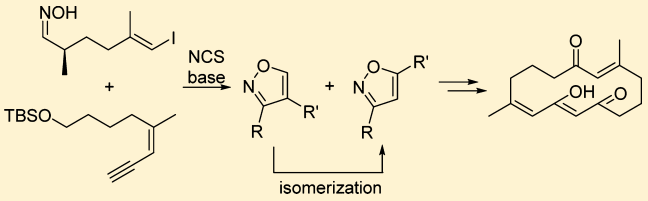
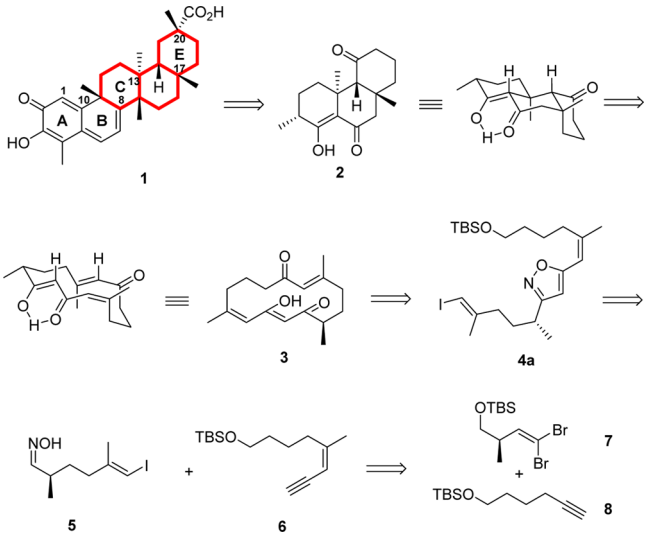
Supporting Information

ABSTRACT: We have developed a convergent synthetic route to an all-carbon, 14-membered *Z,E*-macrocyclic *bis*-enone during our synthetic study of celastrol. The 1,3-dipolar cycloaddition of nitrile oxide and alkyne was employed for fragment coupling and introducing the 1,3-diketone moiety masked in the form of an isoxazole. We discovered that cycloaddition of the nitrile oxide and the enyne gave the rare 3,4-disubstituted isoxazole adduct under kinetic reaction conditions. The cycloaddition was found to be reversible, and the thermodynamic 3,5-disubstituted isoxazole could be obtained by isomerization of its 3,4-disubstituted isomer under elevated temperature. Our mechanistic studies support the role of hydrogen bonding in accelerating the isomerization. Consistent with our previous studies, the *Z,E*-macrocyclic *bis*-enone was found to be inactive toward the transannular *bis*-Michael reaction under the conditions evaluated.



The extracts of *Trypterygium wilfordii* (lei gong teng) have been used in traditional Chinese medicine to treat rheumatoid arthritis for hundreds of years. Recent interest in the extracts' therapeutic effects has led to 14 clinical trials in various stages of completion.[1] One of the active components in the extracts of *T. wilfordii* is celastrol **1** (Scheme 1).[2,3] Studies show that celastrol inhibits the inflammatory response in animal models of lupus, arthritis, amyotrophic lateral sclerosis, and Alzheimer's disease.[4] This compound was also found to induce multiple biological effects at the molecular level, such as NF-κB pathway perturbation, proteasome inhibition, topoisomerase II inhibition, and heat shock response activation.[4] While it is known that celastrol can alter these pathways, the exact molecular target(s) remains unknown. With the opportunity to explore novel biology as well as develop new chemistry, we turned our attention to the synthesis of **1**.

Scheme 1. Retrosynthetic Analysis of Celastrol



Celastrol is representative of a small group of natural quinone methide triterpenoids isolated from the families Celastraceae and Hippocrateaceae.[5] This pentacyclic triterpenoid features an *o*-hydroxy substituted *p*-quinone methide ring system embedded within a **D**:**A**-*freido-nor-oleanane* skeleton. As of now, there is no total synthesis of celastrol in the literature. One of the key structural features of **1** is the perhydrophenanthrene ring system comprising rings C, D, and E. We expected to access this perhydrophenanthrene ring system by a key transannular *bis*-Michael reaction cascade.[6] Therefore, we envisioned that **1** could be accessed by functional group manipulation and installation of the *p*-quinone methide ring system using **2** as the core (Scheme 1). We planned to synthesize the perhydrophenanthrene system **2**, anticipating that the stereochemistry of the angular methyls would be dictated by the olefin geometry of **3** through an all-chair transition state during the transannular reaction. Our retrosynthesis of **3** focused on the use of an isoxazole to rapidly construct the requisite 1,3-diketone through the use of a 1,3-dipolar cycloaddition. Therefore, **3** was envisaged to come from **4a** by desilylation and oxidation of the alcohol to give an aldehyde, intramolecular coupling of that aldehyde with the vinyl iodide, and oxidation to the ketone. This sequence would

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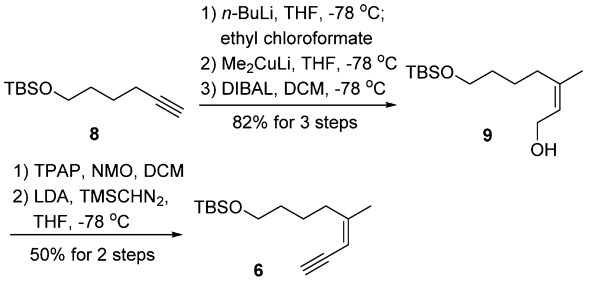
be followed by reduction and hydrolysis of the isoxazole to generate the desired 1,3-diketone functionality. Isoxazole **4a** is expected to come from the intermolecular 1,3-dipolar cycloaddition of enyne **6** and the nitrile oxide derived from oxime **5**. Oxime **5** will be synthesized from the known *gem*-dibromo olefin **7**[7], and enyne **6** will be generated from known TBS silyl ether **8**.[8]

We began our synthesis by constructing the two 1,3-dipolar cycloaddition coupling partners **5** and **6**. Our synthesis of **6** started with the addition of the lithium acetylide derived from **8** to ethyl chloroformate, which generated an alkynyl ester, followed by cupration to install the *Z*-trisubstituted olefin (Scheme 2). These steps were followed with DIBAL reduction

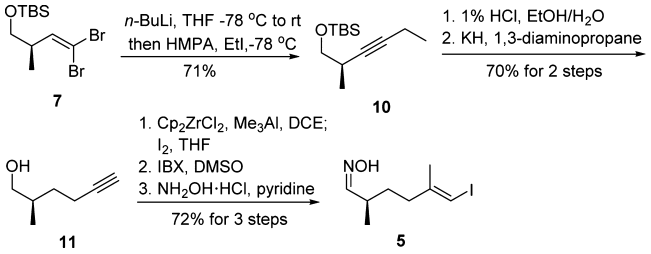
Scheme 2. Synthesis of 6



to give **9** with an 82% yield for three steps. The resulting allylic alcohol **9** was oxidized to an aldehyde using the TPAP/NMO system and then converted to **6** using LDA and $TMSCHN_2$, resulting in a 50% yield over two steps.[9]

The synthesis of oxime **5** began with the known *gem*-dibromo olefin **7** (Scheme 3), which was lithiated with *n*-BuLi

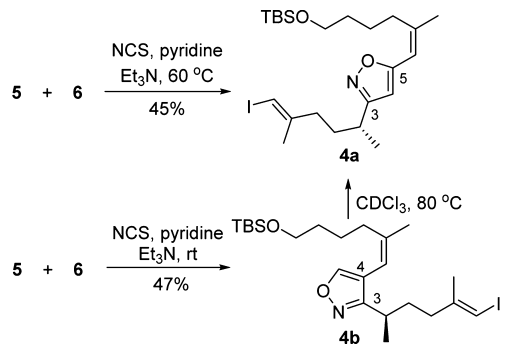
Scheme 3. Synthesis of 5



to form the lithium acetylide. The addition of the resulting acetylide to ethyl iodide required the presence of 2 equiv of HMPA. With the desired internal alkyne synthesized, we performed the KAPA-mediated alkyne zipper reaction using KH and 1,3-diaminopropane. This reaction was uncharacteristically slow with **10** and produced only degradation products. It is known that internal alkynes with a free alcohol are capable of undergoing the KAPA-mediated isomerization.[6a,10] We therefore removed the TBS group and conducted the isomerization reaction on the crude product. External alkyne **11** was obtained with a 70% yield over two steps from internal alkyne **10**. Negishi's carbometalation procedure was then used to install the vinyl iodide.[11] This was followed by IBX oxidation and oxime formation to form the desired oxime **5**, with a 72% yield, from **11**.

With **5** and **6** synthesized, we turned to the 1,3-dipolar cycloaddition for the synthesis of **4a** (Scheme 4). In the course of our evaluation of the reaction, it was discovered that the

Scheme 4. Synthesis of 4a and 4b and Isomerization of 4b to 4a



outcome of the reaction was highly temperature dependent: conducting the reaction at room temperature led to only the 3,4-disubstituted isomer **4b** with a 47% yield. However, elevating the reaction temperature to 60 °C resulted in the production of **4a** with a 45% yield and an approximately 20% yield of **4b**. Curious if we could isomerize **4b** to **4a** given limited examples of reversible 1,3-dipolar cylcoadditions,[12] we heated **4b** to 80 °C. Even though the isomerization was accompanied by partial scrabbling of the C5 alkene (~3:1 desired/undesired), complete conversion of **4b** to the regioisomeric **4a** was observed after 92 h. Both the temperature-dependent regioselectivity of the 1,3-dipolar cycloaddition and the isomerizability of the reaction at elevated temperature are surprising.[13] Sharpless and Fokin, in their study of Cu-catalyzed 1,3-dipolar cycloadditions, examined the activation energies for the formation of regioisomeric 3,4- and 3,5-disubstituted isoxazoles by the uncatalyzed cycloaddition of acetonitrile oxide and propyne.[14] The calculations predicted a 2.8 kcal/mol energy difference in the transition states, with the 3,5-regioisomer being strongly favored. Indeed, formation of 3,4-disubstituted isoxazoles by the 1,3-dipolar cycloaddition of nitrile oxides and alkynes is rare, if not completely unprecedented. However, only the 3,4-disubstituted **4b** was obtained upon reaction of **5** and **6** at room temperature. We speculate that the reversal of regioselectivity is likely due to a substantial increase in the LUMO coefficient at the terminal acetylene carbon of **6** and a concomitant lowering of the LUMO energy due to conjugation of the alkyne.[15] Therefore, due to both the largest orbital coefficient of the nitrile oxide HOMO residing on the oxygen and the largest orbital coefficient of the enyne LUMO residing on the terminal carbon, simple frontier molecular orbital analysis predicts the 3,4-regioisomer to be favored kinetically.

In order to explain the surprising temperature dependence of the regiochemistry of the 1,3-dipolar cycloaddition as well as the slow isomerization of **4b** to **4a** at elevated temperatures, we hypothesized that byproducts from the nitrile oxide synthesis are responsible for this unusual behavior. Chen et al.[16] discovered that hydrogen bond catalysis not only imparted enantiocontrol in the 1,3-dipolar cycloaddition of cyclic enones but also substantially improved the reactivity of the substrate. We postulated that the participation of a hydrogen bond donor (i.e., in situ-generated succinimide) leads to activation of the 3,4-regioisomer and provides a lower energy pathway for the thermodynamically driven isomerization to take place. In order to investigate this hypothesis, we compared the rates of isomerization of **4b** in both the presence and absence of succinimide. Indeed, we found a 1.87-fold increase in the rate of

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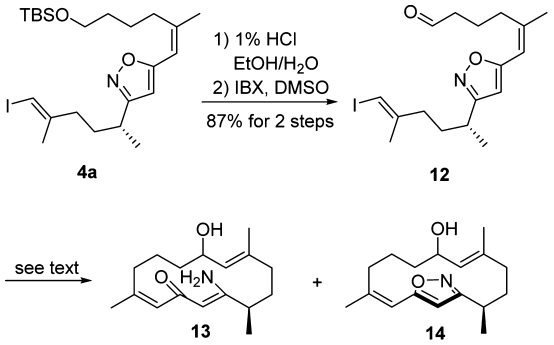
isomerization of **4b** to **4a** in the presence of succinimide at 70 °C.[17]

With a robust means of synthesizing **4a**, we continued in our synthetic studies. We were able to synthesize aldehyde **12** with an 87% yield over two steps from **4a** (Scheme 5). Using the

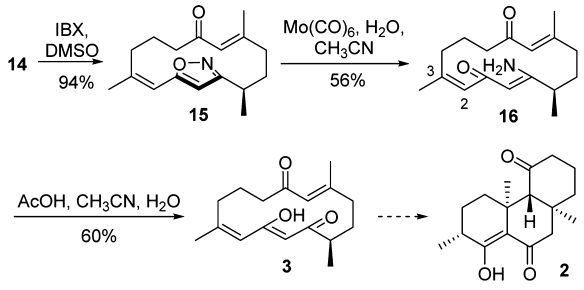
Scheme 5. Synthesis of 14



Nozaki–Hiyama–Kishi reaction,[18] allylic alcohol **14** was formed with a 6–12% yield from **12**. The poor yield of this reaction can be attributed to the formation of a 14-membered macrocycle with a high degree of strain imparted by the alkene functionalities present in the molecule. Also, $CrCl_2$ reductively cleaved the isoxazole in **14**, generating a vinylogous amide **13**. Seeking to keep the isoxazole intact, we reduced the amount of $CrCl_2$ from 10 to 5 equiv. Under such reaction conditions, allylic alcohol **14** was generated in a slightly improved yield (12–26%).

Following the coupling reaction, the resulting allylic alcohol was oxidized to α,β-unsaturated ketone **15** with a 94% yield using IBX (Scheme 6). We turned our attention to revealing

Scheme 6. Synthesis of 3



the 1,3-diketone functional group through reduction and hydrolysis of the isoxazole functionality in **15**. We were pleased to find that the treatment of **15** with $Mo(CO)_6$ in CH_3CN generated the desired vinylogous amide **16** with a 56% yield (2.2:1 *E*/*Z* isomer mixture of the C2–C3 double bond, tentatively assigned by NMR).[19] Alternatively, **16** could be prepared directly from **13** through the action of IBX with a 55% yield. The hydrolysis of **16** to give **3** proved to be difficult. The use of $Cu(OAc)_2$, HOAc/NaOAc, $Mn(OAc)_3$, and $CeCl_3/Et_3N$ all failed to hydrolyze the vinylogous amide. However, when vinylogous amide **16** was dissolved in $AcOH/CH_3CN/H_2O$ (2:2:1), **3** formed with a 60% yield (2.7:1 *E*/*Z* isomer mixture of the C2–C3 double bond, tentatively assigned by NMR).

Our investigation of the transannular *bis*-Michael reaction cascade could then proceed with **3** accessed. In contrast to the smooth transannular Michael reactions when the *E,E*- or *E,Z*-macrocyclic *bis*-enones were employed,[6b] the starting material was fully recovered when **3** was treated with TBAF in THF/DMF at −78 °C. Also, we did not detect any **2** when the reaction was carried out at ambient temperature. We attempted the transannular Michael reactions on vinylogous amide **16** by treatment with NaOMe in DMF. Again, no desired transannular reaction product was detected even when elevated temperatures were applied. These experimental results corroborate our previous work concerning the transannular Michael reaction cascade of 14-membered macrolide systems, which demonstrated that *Z,E*- and *Z,Z*-macrocyclic *bis*-enones are sluggish substrates in transannular *bis*-Michael reactions. Given that our all-carbon macrocycle falls under the *Z,E*-isomer category, it is not surprising that the transannular *bis*-Michael reactions of both **3** and **16** failed to take place.

In summary, as a part of our synthetic study of celastrol, we have developed a synthetic route making use of a 1,3-dipolar cycloaddition for the convergent synthesis of a 1,3-diketone-containing macrocycle. Consistent with our previous studies, this *Z,E*-macrocyclic *bis*-enone was found to be inactive in the transannular *bis*-Michael reaction cascade for the conditions evaluated. We discovered that the 1,3-dipolar cycloaddition of **5** and **6** gave the rare 3,4-disubstituted isoxazole under kinetic reaction conditions. We also demonstrated that the dipolar cycloaddition is reversible, and the thermodynamic 3,5-disubstituted isoxazole can be obtained through isomerization of its 3,4-disubstituted isomer under elevated temperature. Our initial mechanistic studies support the role of hydrogen bonding in accelerating the isomerization process.

EXPERIMENTAL SECTION

General Information. All anhydrous solvents were degassed by bubbling N_2 through the solvents for several hours. The solvents were then dried by passing them through an alumina column before use. Thin layer chromatography was done on TLC silica gel 60 F_{254} commercial plates. NMR spectra were recorded on 500 and 300 MHz spectrometers. All ^1H NMR spectra are referenced to the residual solvent peak (7.26 ppm for $CHCl_3$). All ^{13}C NMR spectra are referenced to the residual solvent peak (77.16 ppm for $CHCl_3$). The chemical shift (δ) of each signal is reported in parts per million (ppm), and all coupling constants (J) are reported in hertz. Molecules **8** and **8–1** were prepared according to the literature.[20,21]

(*Z*)-7-((*tert*-Butyldimethylsilyl)oxy)-3-methylhept-2-en-1-ol (9). MeLi (11.8 mL, 18.8 mmol) was added slowly to a suspension of CuI (1.79 g, 9.42 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at 0 °C until the solution became colorless and homogeneous. The mixture was then cooled to −78 °C, and **8–1** (1.34 g, 4.71 mmol) was added. The mixture was then stirred for 1 h at −78 °C and the reaction quenched with the dropwise addition of a saturated solution of NH_4Cl in 4:1 $EtOH/H_2O$ (10 mL). The reaction was further quenched with 10 mL of saturated (aq) NH_4Cl and allowed to warm to rt. Air was then bubbled into the mixture for 1 h. The mixture was diluted with water (30 mL) and extracted with EtOAc (3 × 50 mL). The organics were dried over $MgSO_4$, filtered, and concentrated. The organics were then flashed through a pad of silica gel (90:10 hexanes/EtOAc) to give **8–2** and used in the next step without further purification. ^1H NMR ($CDCl_3$, 300 MHz): δ 5.65 (s, 1H), 4.13 (q, J = 7.2 Hz, 2H), 3.64–3.59 (m, 2H), 2.63 (t, J = 7.5 Hz, 2H), 1.87 (d, J = 1.2 Hz, 3H), 1.68–1.45 (m, 4H), 1.26 (t, J = 7.2 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

Enoate **8–2** (4.2 mmol crude from the previous step) was azeotroped to dryness with toluene and dissolved in DCM (7.5 mL) under N_2. The mixture was cooled to −78 °C, and DIBAL-H (1.0 M in THF) was added dropwise (10.4 mL, 10.4 mmol). The mixture was stirred for 2 h and the reaction quenched with the careful addition of water (2.5 mL). The mixture was then stirred for 10 min and a 15%

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solution of NaOH in water (10 mL) added, and the mixture was stirred for an additional 10 min. Water was again added (7.5 mL), and the mixture was stirred for 15 min, filtered through a plug of Celite, and dried over $MgSO_4$. The organic phase was then filtered, concentrated, and purified by column chromatography (88:12 hexanes/EtOAc) to give **9** (1.00 g, 82% for 3 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.41 (t, J = 8.5 Hz, 1H), 4.11 (d, J = 7 Hz, 2H), 3.60 (t, J = 6 Hz, 2H), 2.07 (t, J = 7.5 Hz, 2H), 1.72 (s, 3H), 1.51−1.39 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 140.3, 124.4, 63.1, 59.1, 32.6, 31.7, 26.1, 24.6, 23.5, 18.5. HRMS (EI+): m/z calcd for $C_{14}H_{30}LiO_2Si$ $[M + Li]^+$ 265.2175, found: 265.2171.

(*Z*)-7-((*tert*-Butyldimethylsilyl)oxy)-3-methylhept-2-enal (9−1). Allyl alcohol **9** (0.41 g, 1.58 mmol) was dissolved under N_2 in DCM (32 mL) at rt and NMO (0.28 g, 2.4 mmol) and 4 Å molecular sieves (0.44 g) were added. The mixture was cooled to 0 °C and stirred for 1 h. TPAP (16.7 mg, 0.048 mmol) was added, and the mixture was stirred for 15 h and flashed over a silica gel plug (80:20 hexanes/EtOAc) until all product was removed. The product was concentrated to give **9−1** (0.405 g, 100%) as a a colorless oil and was used in the next step without further purification. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.95 (d, J = 8.0 Hz, 1H), 5.88 (d, J = 8.0 Hz, 1H), 3.63 (t, J = 6.0 Hz, 2H), 2.59 (t, J = 7 Hz, 2H), 1.97 (s, 3H), 1.65−1.52 (m, 4H), 0.88 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 190.7, 160.6, 128.5, 62.6, 32.4, 32.3, 25.9, 25.1, 24.9, 18.3, 0.0. HRMS (EI+): m/z calcd for $C_{14}H_{28}LiO_2Si$ $[M + Li]^+$ 263.2019, found: 263.2025

(*Z*)-*tert*-Butyldimethyl((5-methyloct-5-en-7-yn-1-yl)oxy)-silane (6). Diisopropylamine (0.13 mL, 0.94 mmol) was dissolved in THF (6.2 mL) under N_2 and cooled to −78 °C. *n*-BuLi (1.6 M in hexanes, 0.59 mL, 0.94 mmol) was added dropwise, and the mixture was stirred for 15 min. Trimethylsilyldiazomethane (2.0 M in hexanes, 0.47 mL, 0.94 mmol) was added dropwise, and the mixture was stirred at −78 °C for 30 min. **9−1** (0.2 g, 0.78 mmol) in THF (1.6 mL) was added dropwise, and the mixture was left to slowly warm to rt over the course of 1 h. After 10 min at rt, the reaction was quenched with water (6 mL) and the mixture stirred for 10 min. The mixture was then extracted with EtOAc (3 × 25 mL). The organics were dried over $MgSO_4$, filtered, and concentrated. The material was purified by column chromatography (97:3 hexanes/EtOAc) to give **6** (120 mg, 50% for 2 steps) as a light yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.26 (s, 1H), 3.63 (t, J = 6.0 Hz, 2H), 2.96 (s, 1H), 2.34 (t, J = 7.5 Hz, 2H), 1.79 (d, J = 1.0 Hz, 3H), 1.57−1.48 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 154.7, 104.6, 81.8, 79.3, 63.0, 34.4, 32.5, 26.1, 23.8, 22.5, 18.5, 0.2. HRMS (EI+): m/z calcd for $C_{15}H_{29}OSi$ $[M + H]^+$ 253.1982, found: molecular ion not observed.

(±)-*tert*-Butyldimethyl((2-methylhex-3-yn-1-yl)oxy)silane (10). Dibromide **7** (0.25 g, 0.7 mmol) was dissolved in THF (6.5 mL) and cooled to −78 °C under N_2. *n*-BuLi (0.96 mL, 1.54 mmol, 1.6 M in hexanes) was added dropwise, and the mixture was stirred at −78 °C for 1 h. The mixture was then stirred at rt for 1 h. The mixture was cooled to 0 °C, and HMPA (0.24 mL, 1.4 mmol) was added. The mixture was cooled to −78 °C, and ethyl iodide (0.28 mL, 3.5 mmol) was added; the mixture was stirred for 6 h while warming to rt. The reaction was quenched with saturated NH_4Cl (1 mL) and the mixture diluted with water. The product was then extracted with EtOAc (3 × 30 mL), and the organics were dried over $MgSO_4$, filtered, and concentrated. The material was purified by column chromatography (96:4 hexanes/EtOAc) to give **10** (113 mg, 71%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.67−3.64 (m, 1H), 3.41−3.38 (m, 1H), 2.55−2.50 (m, 1H), 2.18−2.13 (m, 2H), 1.13−1.09 (m, 6H), 0.89 (s, 9H), 0.06 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 82.6, 81.5, 67.6, 29.1, 25.9, 18.6, 17.7, 14.3, 12.4, 0.0. HRMS (EI+): m/z calcd for $C_{13}H_{26}LiOSi$ $[M + Li]^+$ 233.1913, found: 233.1924.

(±)-2-Methylhex-5-yn-1-ol (11). Alkyne **10** (0.46 g, 2.0 mmol) was dissolved in 1% HCl in 95:5 EtOH/H_2O (29 mL). The mixture was stirred for 20 min and the reaction quenched with saturated $NaHCO_3$ (20 mL). The mixture was diluted with H_2O (50 mL) and extracted with ether (3 × 70 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated to give 0.39 g of crude material. The material was used without purification.

In a glovebox, a flask was charged with KH (0.97 g) that had been washed with hexanes to rid the KH of mineral oil. This flask was taken from the glovebox and placed under N_2 on a Schlenk line. 1,3-Diaminopropane (20.2 mL) was added to the flask, and the mixture was heated with a heat gun until foaming occurred. The mixture was then stirred at rt for 1 h. **10−1** (∼2.0 mmol from the previous step) in 1 mL of 1,3-diaminopropane was added to the mixture at rt, and the mixture was stirred for 19 h with monitoring by NMR. After NMR indicated the reaction was complete, the mixture was cooled to 0 °C and the reaction quenched with the careful addition of saturated NH_4Cl (20 mL). The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3 × 50 mL). The organics were dried over $MgSO_4$, filtered, and concentrated. The material was purified by column chromatography (60:40 hexanes/EtOAc) to give **11** (158 mg, 70% for 2 steps) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.54−3.46 (m, 2H), 2.32−2.18 (m, 2H), 1.94 (t, J = 3.0 Hz, 1H), 1.82−1.76 (m, 1H), 1.72−1.65 (m, 1H), 1.46 (brs, 1H), 1.41−1.34 (m, 1H), 0.94 (d, J = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 84.6, 68.5, 67.8, 34.9, 31.9, 16.3, 16.2. HRMS (EI+): m/z calcd for $C_7H_{13}O$ $[M + H]^+$ 113.0961, found: molecular ion not observed.

(±)-(5*E*)-6-Iodo-2,5-dimethylhex-5-enal Oxime (5). Cp_2ZrCl_2 (0.39 g, 1.3 mmol) was dissolved in $(CH_2Cl)_2$ (2 mL) under N_2, and Me_3Al (2.0 M in toluene, 1.9 mL, 3.8 mmol) was added at rt. The mixture was stirred for 15 min, and **11** (0.15 g, 1.3 mmol) in $(CH_2Cl)_2$ (0.4 mL) was added dropwise at 0 °C. The mixture was stirred and allowed to warm to rt over the course of 2 h. After TLC indicated carbometalation was complete, the mixture was cooled to 0 °C, and I_2 (0.42 g, 1.66 mmol) in THF (2 mL) was added dropwise. The mixture was warmed to rt and stirred for 10 min. The reaction was quenched with the dropwise addition of NH_4Cl (20 mL). Water (10 mL) was then added, and the mixture was extracted with diethyl ether (3 × 50 mL). The organics were dried over $MgSO_4$, filtered, and concentrated. The material was then flashed over a short silica gel plug to remove inorganic impurities (40:60 hexanes/Et_2O). The material was then concentrated to give **11−1** as a light yellow oil and used in the next step. Yields varied from 76 to 34%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.90−5.89 (m, 1H), 3.53−3.44 (m, 2H), 2.31−2.18 (m, 1H), 1.84 (d, J = 1.0 Hz, 3H), 1.63−1.56 (m, 2H), 1.28−1.21 (m, 2H), 0.93 (d, J = 6.5 Hz, 3H).

Alcohol **11−1** (1.20 g, 4.71 mmol) was dissolved in DMSO (87 mL), and IBX (1.98 g, 7.07 mmol) was added. The mixture was stirred for 15 h, the reaction was quenched with the addition of H_2O (100 mL), and the mixture was stirred for 8 min. The slurry was filtered over a pad of Celite, and the Celite was rinsed with ether (100 mL). The filtrate was diluted with brine (20 mL), and the organic phase was removed. The aqueous phase was extracted with ether (75 mL), and the organics were combined, dried over Na_2SO_4, filtered, and concentrated to give a colorless oil.

Aldehyde **11−2** (∼1.20 g, 4.71 mmol) was dissolved in pyridine (13 mL), and NH_2OH·HCl (0.43 g, 6.12 mmol) was added at rt. The mixture was stirred for 30 min and poured into ether (12 mL). The organic mixture was washed with a saturated solution of $CuSO_4$ and water. The organic phase was then dried over Na_2SO_4, filtered, and concentrated to give **5** (1.17 g, 95% yield for 2 steps) as a viscous yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.28 (d, J = 6.9 Hz, 0.8H), 6.49 (d, J = 7.8 Hz, 0.2H), 5.92−5.90 (m, 1H), 2.39−2.30 (m, 1H), 1.84−1.83 (m, 3H), 2.23 (t, J = 7.2 Hz, 2H), 1.67−1.25 (m, 2H), 1.25 (brs, 1H), 1.10−1.08 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 156.9, 155.9, 147.4, 75.4, 37.3, 37.0, 34.0, 32.8, 32.6, 29.8, 29.1, 24.0, 18.1, 17.6. LRMS (EI+): m/z calcd for $C_8H_{15}INO_2$ $[M + H]^+$ 268.0193, found 268.0240. HRMS (EI+): m/z calcd for $C_8H_{15}INO_2$ $[M + H]^+$ 268.0193, found not observed.

(±)-5-((*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-methylhex-1-en-1-yl)-3-((*E*)-6-iodo-5-methylhex-5-en-2-yl)isoxazole (4a). Oxime **5** (1.17 g, 4.38 mmol) was dissolved in $CHCl_3$ (2.8 mL) and added dropwise to a solution of NCS (0.585 g, 4.38 mmol) and pyridine (7 μL, 0.09 mmol) in $CHCl_3$ (2.8 mL). The mixture was stirred until the solid disappeared (∼20 min), and **6** (1.33 g, 5.3 mmol) in $CHCl_3$ (2.8

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mL) was added in one portion. A solution of Et_3N (0.62 mL, 4.38 mmol) in $CHCl_3$ (11.4 mL) was added slowly, and the mixture was heated to 60 °C overnight. The mixture was then cooled to rt and washed with water, $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The material was purified by column chromatography (90:10 hexanes/EtOAc) to give **4a** (1.01 g, 45%) as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.11 (s, 1H), 5.88−5.87 (m, 2H), 3.65−3.61 (m, 2H), 2.91−2.83 (m, 1H), 2.49−2.42 (m, 2H), 2.24−2.14 (m, 2H), 1.93 (d, J = 1.2 Hz, 3H), 1.82 (d, J = 1.2 Hz, 3H), 1.80−1.68 (m, 2H), 1.60−1.51 (m, 4H), 1.27 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.7, 167.8, 147.8, 147.5, 112.0, 99.6, 75.3, 63.0, 37.2, 34.4, 34.3, 33.6, 32.6, 31.3, 26.1, 24.6, 24.2, 24.1, 20.2, 18.5, −5.1. HRMS (EI+): m/z calcd for $C_{23}H_{40}LiINO_2Si$ $[M + Li]^+$ 524.2033, found 524.2017.

(±)-4-((*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-methylhex-1-en-1-yl)-3-((*E*)-6-iodo-5-methylhex-5-en-2-yl)isoxazole (4b). Oxime **5** (134 mg, 0.51 mmol) was dissolved in $CHCl_3$ (0.33 mL) and added dropwise to a solution of NCS (68 mg, 0.51 mmol) and pyridine (1 μL, 0.01 mmol) in $CHCl_3$ (0.33 mL). The mixture was stirred until the solid disappeared (∼20 min), and **6** (0.154 g, 0.61 mmol) in $CHCl_3$ (0.33 mL) was added in one portion. A solution of Et_3N (72 μL, 0.51 mmol) in $CHCl_3$ (1.3 mL) was added slowly, and the mixture was stirred overnight at rt. The mixture was then washed with water, $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4, filtered, and concentrated. The material was purified by column chromatography (80:20 hexanes/EtOAc) to give **4b** (0.125 g, 47%) as a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz): δ 8.02 (brs, 1H), 5.90−5.88 (m, 1H), 5.23 (d, J = 1.5 Hz, 1H), 3.64−3.60 (m, 2H), 2.61−2.37 (m, 3H), 2.19 (t, J = 7.5 Hz, 2H), 1.86 (d, J = 1.2 Hz, 3H), 1.82 (d, J = 0.9 Hz, 3H), 1.81−1.69 (m, 1H), 1.57−1.50 (m, 5H), 1.17 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.6, 148.1, 147.5, 104.7, 100.6, 75.3, 63.1, 38.8, 38.1, 37.2, 35.2, 32.8, 32.7, 32.4, 26.1, 24.1, 23.9, 23.0, 19.0, 18.5. HRMS (EI+): m/z calcd for $C_{23}H_{40}LiINO_2Si$ $[M + Li]^+$ 524.2033, found 524.2014.

Thermal Isomerization of 4b to 4a. Isoxazole **4b** (8.3 mg, 0.016 mmol) was dissolved in $CDCl_3$ (0.7 mL) and placed in an NMR tube. The tube was wrapped thoroughly with Parafilm. The mixture was heated to 80 °C and followed by NMR. Analysis by NMR indicated that conversion of **4b** to **4a** was complete after 92 h. Also, it was observed that olefin isomerization occurred with a 3:1 desired/undesired ratio. TLC analysis indicated that the olefin isomers were inseparable.

(±)-(*Z*)-6-(3-((*E*)-6-Iodo-5-methylhex-5-en-2-yl)isoxazol-5-yl)-5-methylhex-5-enal (12). Isoxazole **4a** (0.125 g, 0.24 mmol) was dissolved in 3.3 mL of 1% HCl in 95:5 EtOH/H_2O, and the mixture was stirred for 20 min. The reaction was quenched with the addition of saturated $NaHCO_3$ (1.5 mL) and the mixture diluted with water (7 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL), and the organics were dried over Na_2SO_4, filtered, and concentrated. The crude material was used in the next step without further purification. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.10 (s, 1H), 5.89−5.87 (m, 2H), 3.71−3.67 (m, 2H), 2.90−2.83 (m, 1H), 2.49−2.45 (m, 2H), 2.23−2.13 (m, 2H), 1.94 (d, J = 1.2 Hz, 3H), 1.81 (d, J = 0.9 Hz, 3H), 1.79−1.68 (m, 3H), 1.66−1.55 (m, 4H), 1.26 (d, J = 7.2 Hz, 3H).

Isoxazole **4a**−**1** (0.24 mmol from the previous step) was dissolved in DMSO (0.7 mL), and IBX (102 mg, 0.36 mmol) was added. The mixture was stirred for 20 h and the reaction quenched with the addition of water (2 mL). The slurry was stirred for 15 min and then filtered over Celite. The Celite was washed with EtOAc (3 × 10 mL). The filtrate was dried over $MgSO_4$ and concentrated. The material was purified by column chromatography (the first neutralization was with 1% Et_3N in hexanes, then the column was run with 85:15 hexanes/EtOAc) to give **12** (84 mg, 87% for 2 steps) as a yellow residue. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.80−9.79 (m, 1H), 6.13 (s, 1H), 5.98 (s, 1H), 5.87 (s, 1H), 2.91−2.84 (m, 1H), 2.56−2.45 (m, 4H), 2.26−2.13 (m, 2H), 2.94 (s, 3H), 1.90−1.65 (m, 4H), 1.81 (s, 3H), 1.27 (d, J = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.2, 168.3, 138.0, 147.5, 146.3, 112.6, 100.1, 75.3, 43.6, 37.2, 34.2, 33.3, 31.2, 24.9, 24.1, 20.2, 20.1. HRMS (EI+): m/z calcd for $C_{17}H_{24}LiINO_2$ $[M + Li]^+$ 408.1012, found 408.0991.

(±)-(2*Z*,7*E*,13*Z*)-3-Amino-9-hydroxy-4,7,13-trimethylcyclotetradeca-2,7,13-trienone (13). In a glovebox, $CrCl_2$ (0.255 g, 2.09 mmol) and $NiCl_2$ (2.7 mg, 0.021 mmol) were combined in a flame-dried flask. The flask was placed under N_2 on a Schlenk line. THF (0.24 mL) was added to the mixture of $CrCl_2$ and $NiCl_2$. **12** (84 mg, 0.21 mmol) was dissolved in DMF (21 mL), and the resulting solution was cannulated at rt to the flask containing $CrCl_2$, $NiCl_2$, and THF. The mixture was then stirred at rt for 20 h and the reaction quenched with the addition of a potassium serinante solution (7 mL).[22] The mixture was stirred for 1 h, and the DMF was removed in vacuo. The resulting solids were partitioned between 50 mL of water and 125 mL of EtOAc. The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 125 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. The material was purified by column chromatography (50:50 to 40:60 hexanes/EtOAc) to give **13** (7 mg, 12% as a 1:1.5 mixture of diastereomers) as a sticky residue. ^1H NMR ($CDCl_3$, 300 MHz): δ 9.95 (brs, 1H), 5.75 (s, 0.6H), 5.72 (s, 0.4H), 5.39 (d, J = 8.1 Hz, 0.4H), 5.24 (d, J = 8.7 Hz, 0.6H), 5.13 (s, 0.6H), 5.11 (s, 0.4H), 4.99 (brs, 1H), 4.44−4.35 (m, 1H), 22.55−1.96 (m, 4H), 1.93−1.45 (m, 7H), 1.78−1.77 (m, 3H), 1.72 (s, 1.2H), 1.65 (s, 1.8H), 1.33 (brs, 1H), 1.18−1.15 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 193.23, 193.17, 169.5, 168.1, 144.2, 144.1, 139.8, 139.5, 129.8, 129.3, 129.2, 129.1, 97.1, 96.7, 67.9, 67.2, 45.9, 41.2, 40.2, 39.1, 37.0, 36.8, 36.4, 35.2, 33.6, 31.7, 31.0, 24.4, 24.1, 23.3, 21.7, 15.5, 8.8. HRMS (EI+): m/z calcd for $C_{17}H_{27}LiNO_2$ $[M + Li]^+$ 284.2202, found 284.2195.

(±)-(5*E*,11*Z*)-2,5,11-Trimethyl-14-oxa-15-azabicyclo[11.2.1]hexadeca-1(15),5,11,13(16)-tetraen-7-ol (14). In a glovebox, $CrCl_2$ (46 mg, 0.37 mmol) and $NiCl_2$ (∼1 mg, 0.008 mmol) were combined in a flame-dried flask. The flask was placed under N_2 on a Schlenk line. THF (84 μL) was added to the mixture of $CrCl_2$ and $NiCl_2$. **12** (30 mg, 0.075 mmol) was dissolved in DMF (7.5 mL), and the resulting solution was cannulated at rt to the flask containing $CrCl_2$, $NiCl_2$, and THF. The mixture was then stirred at rt for 21 h and the reaction quenched with the addition of a potassium serinante solution (2.5 mL).[21] The mixture was stirred for 1 h, and the DMF was removed in vacuo. The resulting solids were partitioned between 18 mL of water and 45 mL of EtOAc. The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 45 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. The material was purified by column chromatography (70:30 to 50:50 hexanes/EtOAc) to give **14** (4.7 mg, 23% as a 1:2.1 mixture of diastereomers) as a sticky residue. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.09 (s, 0.3H), 6.06 (s, 0.7H), 6.00 (s, 0.3H), 5.91 (s, 0.7H), 5.13 (d, J = 9.0 Hz, 0.3H), 5.03 (d, J = 9.0 Hz, 0.7H), 4.32−4.19 (m, 1H), 3.11−3.00 (m, 0.3H), 2.92−2.81 (m, 0.7H), 2.52−2.31 (m, 1H), 2.19−1.64 (m, 5H), 1.92−1.90 (m, 3H), 1.52 (s, 2.1H), 1.47 (s, 0.9H), 1.45−1.15 (m, 4H), 1.30−1.26 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.9, 167.7, 149.0, 148.5, 140.1, 139.5, 128.3, 127.5, 112.3, 112.1, 101.4, 101.2, 68.1, 68.0, 39.0, 36.9, 36.6, 35.1, 34.3, 34.1, 33.9, 32.9, 32.2, 32.1, 26.1, 25.9, 22.6, 22.3, 21.7, 20.1, 17.8, 15.9. HRMS (EI+): m/z calcd for $C_{17}H_{25}LiNO_2$ $[M + Li]^+$ 282.2045, found 282.2051.

(±)-(5*E*,11*Z*)-2,5,11-Trimethyl-14-oxa-15-azabicyclo[11.2.1]hexadeca-1(15),5,11,13(16)-tetraen-7-one (15). Isoxazole **14** (24 mg, 0.087 mmol) was dissolved in DMSO (1.0 mL), and IBX (36.5 mg, 0.13 mmol) was added in one portion. The mixture was stirred at rt for 16 h. The reaction was quenched with the addition of H_2O (1.2 mL) and the mixture stirred for 15 min. The slurry was filtered through a plug of Celite, and the plug was washed with EtOAc. The filtrate was dried over Na_2SO_4 and concentrated. The material was purified by column chromatography (90:10 to 80:20 hexanes/EtOAc) to give **15** (22.4 mg, 94%) as a pale yellow residue. ^1H NMR ($CDCl_3$, 300 MHz): δ 6.09 (s, 1H), 5.84 (s, 1H), 5.54 (s, 1H), 2.99−2.87 (m, 1H), 2.34−2.17 (m, 5H), 2.08 (d, J = 0.9 Hz, 3H), 2.08−1.98 (m, 1H), 1.91 (d, J = 1.5 Hz, 3H), 1.86−1.67 (m, 4H), 1.27 (d, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.1, 168.0, 167.3, 158.8, 147.9, 124.2, 112.9, 101.9, 42.0, 38.9, 32.8, 32.4, 31.9, 24.5, 23.1, 21.1, 19.3. HRMS (EI+): m/z calcd for $C_{17}H_{23}LiNO_2$ $[M + Li]^+$ 280.1889, found 280.1890.

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(±)-(2*Z*,8*E*,13*Z*)-13-Amino-3,9,12-trimethylcyclotetradeca-2,8,13-triene-1,7-dione (16). Isoxazole **15** (9.5 mg, 0.035 mmol) was dissolved in CH_3CN (0.7 mL) under N_2 in a 1.5 mL flame-dried bomb. To this solution was added H_2O (1 μL) followed by $Mo(CO)_6$ (4.7 mg, 0.018 mmol). The mixture was sealed, heated to 80 °C, and stirred for 40 min. The solution was concentrated, and the material was purified by column chromatography (60:40 hexanes/EtOAc) to give **16** (3.7 mg, 56%, 2.2:1 *E*/*Z* isomer mixture by NMR) as a sticky residue. The spectra were consistent with material previously prepared using the alternate synthesis of **16**. See Alternate Synthesis of 16 for spectral analysis.

Alternate Synthesis of 16. Vinylogous amide **13** (6.1 mg, 0.022 mmol) was dissolved in DMSO (0.35 mL) at rt, and IBX (9.2 mg, 0.033 mmol) was added. The mixture was stirred for 8 h and the reaction quenched with the addition of 0.36 mL of water. The mixture was stirred for 15 min, and then the slurry was filtered over Celite. The Celite was washed with EtOAc, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The organic phases were dried over Na_2SO_4, filtered, and concentrated. The material was purified by column chromatography (60:40 hexanes/EtOAc) to give **16** (4.7 mg, 55%) as a sticky residue. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.97 (brs, 1H), 6.15 (s, 1H), 5.85 (s, 1H), 5.13 (s, 1H), 4.91 (brs, 1H), 2.15−2.27 (m, 5H), 2.26−2.08 (m, 2H), 2.15 (s, 3H), 1.89−1.65 (m, 4H), 1.79 (s, 3H), 1.17 (d, *J* = 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.9, 192.4, 167.7, 156.9, 145.0, 129.9, 125.1, 97.3, 43.4, 40.4, 39.8, 32.2, 30.1, 24.3, 23.4, 21.4, 18.1. HRMS (EI+): *m*/*z* calcd for $C_{17}H_{26}NO_2$ $[M + H]^+$ 276.1964, found 276.1956.

(±)-(2*Z*,8*E*,13*Z*)-13-Hydroxy-3,9,12-trimethylcyclotetradeca-2,8,13-triene-1,7-dione (3). Vinylogous amide **16** (3.0 mg, 0.012 mmol) was dissolved in AcOH (0.1 mL). Water (50 μL) followed by CH_3CN (0.1 mL) was added to this solution. The mixture was stirred at rt for 6 h and diluted with DCM (1 mL) and water (1 mL). The aqueous phase was washed with DCM (3 × 3 mL), and the organic phases were combined, dried over Na_2SO_4, and concentrated. The material was purified by column chromatography (88:12 hexanes/EtOAc) to give **3** (1.7 mg, 60% 2.7:1 *E*/*Z* isomer mixture) as a white residue. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 15.63−15.54 (m, 1H), 5.97 (s, 1H), 5.81 (s, 0.7H), 5.78 (s, 0.3H), 5.50 (s, 1H), 2.75−2.65 (m, 1H), 2.38−2.20 (m, 5H), 2.16 (d, *J* = 1.2 Hz, 2H), 2.10−1.94 (m, 3H), 1.87 (d, *J* = 1.2 Hz, 1H), 1.83 (d, *J* = 1.2 Hz, 3H), 1.71−1.61 (m, 2H), 1.13−1.08 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 200.2, 199.8, 158.7, 151.0, 125.0, 124.5, 124.2, 123.7, 101.4, 100.9, 43.6, 43.5, 42.1, 41.6, 40.8, 39.8, 32.5, 31.3, 31.1, 31.0, 30.8, 29.8, 27.9, 26.1, 24.5, 24.4, 22.7, 22.0, 19.5, 19.1, 18.4. HRMS (EI+): *m*/*z* calcd for $C_{17}H_{25}O_3$ $[M + H]^+$ 277.1804, found 277.1806.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) U.S. National Institutes of Health. *United States Clinical Trials Online Registry*; National Institutes of Health: Bethesda, MD. http://clinicaltrials.gov/ct2/results?term=tripterygium+wilfordii (accessed February 12, 2013).

(2) Chou, T. Q.; Mei, P. E. *Zhongguo Shenglixue Zazhi* **1936**, *10*, 529−534.

(3) Harada, R.; Kakisawa, H.; Kobayashi, S.; Musya, M.; Nakanishi, K.; Takahashi, Y. *Tetrahedron Lett.* **1962**, *3*, 603−607.

(4) Sethi, G.; Ahn, K. S.; Pandey, M. K.; Aggarwal, B. B. *Blood* **2007**, *109*, 2727−2735.

(5) (a) Setzer, W. N.; Setzer, M. C. *Mini−Rev. Med. Chem.* **2003**, *3*, 540−556. (b) Alvarenga, N.; Ferro, E. A. *Stud. Nat. Prod. Chem.* **2005**, *30*, 635−702. (c) Zhou, Q. Natural Diterpene and Triterpene Quinone Methides: Structures, Synthesis and Biological Potentials. In *Quinone Methides*; Rokita, S. E., Ed.; Wiley: Hoboken, NJ, 2009.

(6) (a) Scheerer, J. R.; Lawrence, J. F.; Wang, G. C.; Evans, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 8968−8969. (b) Xue, H.; Gopal, P.; Yang, J. *J. Org. Chem.* **2012**, *77*, 8933−8945. (c) Xue, H.; Yang, J.; Gopal, P. *Org. Lett.* **2011**, *13*, 5696−5699. (d) Yang, J.; Xue, H. Transannular Cyclization in Natural Product Total Synthesis. In *Stereoselective Synthesis of Drugs and Natural Products*; Andrushko, V., Andrushko, N., Eds.; Wiley: Hoboken, NJ, 2013.

(7) Kalesse, M.; Chary, K. P.; Quitschalle, M.; Burzlaff, A.; Kasper, C.; Scheper, T. *Chem.—Eur. J.* **2003**, *9*, 1129−1136.

(8) Negishi, E.-i.; Pour, M.; Cederbaum, F. E.; Kotora, M. *Tetrahedron* **1998**, *54*, 7057−7074.

(9) Nicolaou, K. C.; Nold, A. L.; Milburn, R. R.; Schindler, C. S. *Angew. Chem., Int. Ed.* **2006**, *45*, 6527−6532.

(10) Lindhoudt, J. C.; van Mourik, G. L.; Pabon, H. J. J. *Tetrahedron Lett.* **1976**, *17*, 2565−2568.

(11) Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639−6647.

(12) (a) Kritchenkov, A. S.; Bokach, N. A.; Kuznetsov, M. L.; Dolgushin, F. M.; Tung, T. Q.; Molchanov, A. P.; Kukushkin, V. Y. *Organometallics* **2012**, *31*, 687−699. (b) Nakayama, J.; Kaneko, A.; Sugihara, Y.; Ishii, A.; Oishi, A.; Shibuya, I. *Heteroat. Chem.* **2000**, *11*, 434−440.

(13) Heaney, F. *Eur. J. Org. Chem.* **2012**, 3043−3058.

(14) Himo, F.; Lovell, T.; Hilgraf, R.; Rostovtsev, V. V.; Noodleman, L.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 210−216.

(15) Houk, K. N. *Acc. Chem. Res.* **1975**, *8*, 361−369.

(16) Chen, W.; Du, W.; Duan, Y.-Z.; Wu, Y.; Yang, S.-Y.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 7667−7670.

(17) The experimental design is as follows. Two NMR tubes were each charged with 0.5 mL of $CDCl_3$ containing 6.5 mg of **5b** (0.013 mmol). Succinimide was added to one of the tubes (6.2 mg, 0.063 mmol). Both NMR tubes were sealed and heated to 70 °C and held at that temperature for 2 days. The reaction progress was analyzed by NMR at 2, 4, 18, 25, and 41 h. The relative abundance of **5a** for each tube was determined, and the rate enhancement was calculated by dividing the relative abundance of **5a** in the presence of succinimide by the relative abundance of **5a** in only $CDCl_3$.

(18) Pospíšil, J.; Müller, C.; Fürstner, A. *Chem.—Eur. J.* **2009**, *15*, 5956−5968.

(19) Nitta, M.; Kobayashi, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1401−1406.

(20) Guo, H.; Mortensen, M. S.; O'Doherty, G. A. *Org. Lett.* **2008**, *10*, 3149−3152.

(21) See the Supporting Information for the structures of some synthetic intermediates (**8−1**, **8−2**, **9−1**, **10−1**, **11−1**, **11−2**, and **4a−1**).

(22) The potassium serinate solution was prepared by mixing 6.59 g of serine, 4.71 g of $KHCO_3$, and 3.25 g of K_2CO_3 in 55 mL of H_2O.