JOC The Journal of Organic Chemistry

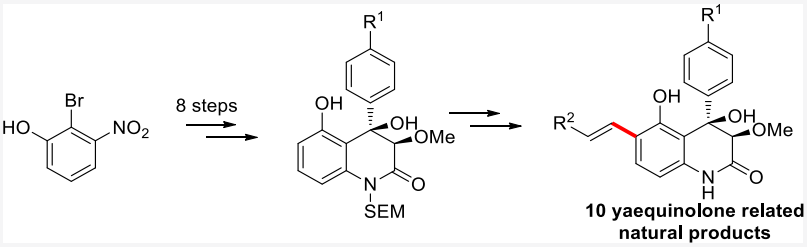
pubs.acs.org/joc Article

Divergent Total Syntheses of Yaequinolone-Related Natural Products by Late-Stage C−H Olefination

Wen-Liang Jia, Sabela Vega Ces, and M. Ángeles Fernández-Ibáñez*

Cite This: J. Org. Chem. 2021, 86, 6259−6277 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: Divergent total syntheses of 10 yaequinolone-related natural products have been achieved for the first time by late-stage C−H olefination of 3,4-dioxygenated 4-aryl-5-hydroxyquinolin-2(1*H*)-ones, core structures of this family of natural products. A robust synthetic methodology to construct the core structures has been established, and the C−H olefination reaction has been carried out with synthetically useful yields and high levels of site-selectivity under mild reaction conditions in the presence of a Pd/S,O-ligand catalyst.

INTRODUCTION

Yaequinolones and related compounds that comprise 3,4-dioxygenated 4-aryl-quinolin-2(1*H*)-one cores represent a growing family of biologically active alkaloids isolated from marine and plant fungi (Figure 1a).[1] The first two members, NTC-47A and B, were isolated from the second metabolites of *Penicillium* sp. by Nakaya in 1995 and they showed promising insecticidal activities.[2] Since then, many more related compounds have been discovered and their structures, bioactivities, and biosynthetic mechanisms have been intensively studied.[3−6] Structurally, the two oxygenated functional groups at 3- and 4-positions have a cis-configuration for most of the members.[7] Moreover, the majority of these natural products possess a hydroxyl group at the 5-position and only differ from each other in the olefin moiety present at the 6-position (Figure 1b).

This family of natural products has attracted great attention in the last few years due to their unique structures and biological activities, and the total syntheses of few members of this family of natural products have been reported. The first total synthesis of this family of natural products was the synthesis of (±)-yaequinolone A2, the structurally simplest molecule among the family (Scheme 1a).[8] The key step of this approach is the intramolecular aldol reaction of N-glycolated 2-aminobenzophenone to construct the quinolone core, generating the two oxygenated functional groups in a cis-fashion. The first enantioselective total syntheses of (−)-yaequinolones J1 and J2 were reported in 2018 by the group of Hanessian (Scheme 1b).[9] The authors used an Evans-type chiral auxiliary to provide the *syn*-aldol diol as a 1:1 mixture of diastereoisomers that differ in the configuration of the pyranyl tertiary methyl group. The group of Christmann successfully synthesized (±)-peniprequinolone, (±)-aflaquinolones E and F, (±)-6-deoxyaflaquinolone E, (±)-quinolinones A and B, and (±)-aniduquinolone C by developing a general method for the construction of N-glycolated 2-aminobenzophenone via aryne insertions into unsymmetrical imides in flow (Scheme 1c).[10]

In spite of this progress, a general strategy to access these natural products in a direct and divergent manner is still elusive.[11] As many members of this family of natural products (>20) only differ from each other in the structure of the olefin at the 6-position, we envisioned that their syntheses can be achieved from a key common intermediate in a divergent manner using late-stage site-selective C−H olefination.[12] Herein, we report a new methodology for the late-stage C(6)−H olefination of 3,4-dioxygenated 4-aryl-5-hydroxyquinolin-2(1*H*)-ones and its successful application in the divergent total syntheses of 10 yaequinolone-related natural products, which are synthesized for the first time (Scheme 1d).

Received: January 6, 2021
Published: April 22, 2021

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

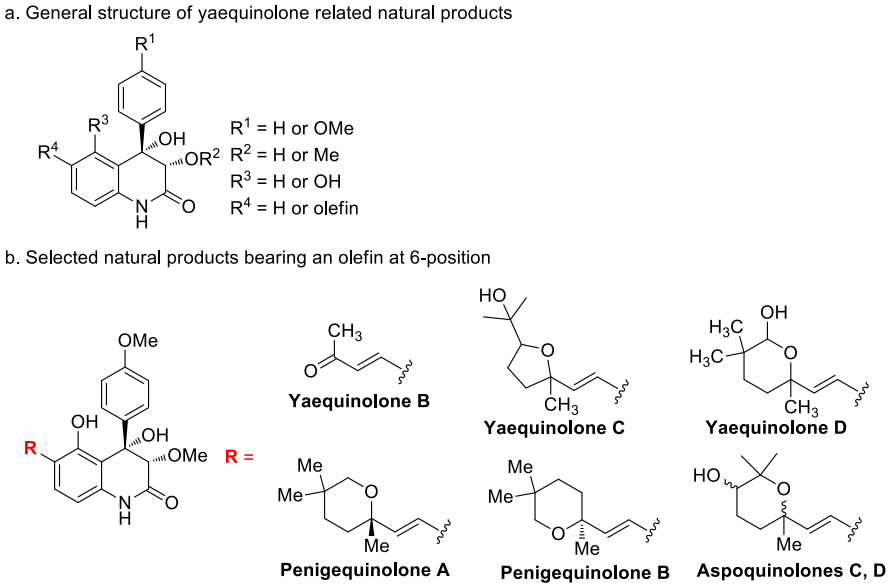


Figure 1. Structures of yaequinolone-related natural products.

RESULTS AND DISCUSSION

In 2019, we reported a highly selective C(6)−H olefination reaction of tetrahydroquinolines (THQs) in the presence of a Pd/S,O-ligand catalyst (Scheme 2a).[13] We hypothesized that late-stage selective C(6)−H olefination of 3,4-dioxygenated 4-aryl-5-hydroxy-quinolin-2(1*H*)-one cores could be developed in the presence of a Pd/S,O-ligand catalyst to directly access yaequinolone-related natural products in a divergent manner.

First, we evaluated the C−H olefination reaction of *N*-methyl-3,4-dihydroquinolin-2(1*H*)-one (**1a**), the simplified backbone of yeaquinolone-related natural products, with ethyl acrylate under reported reaction conditions for the olefination of THQs. As expected, because the aromatic ring is less activated,[13,14] the reaction only provided the olefinated product in less than 10% ^{1}H NMR yield (Scheme 2b). When the reaction was performed at 80 °C, a slightly higher yield of 23% was achieved (Scheme 2b).

Because all our target natural products have a hydroxyl group at the 5-position, we decided to investigate the effect of this functional group on the reactivity of the C−H olefination of quinolin-2(1*H*)-ones. We tested *N*-methyl-3,4-dihydro-2(1*H*)-quinolinones bearing an OMe, OEt, or/and OMOM group at the 5-position (**2a**−**4a**, Scheme 3). As expected, because these substrates are more activated, synthetically useful yields (45−57%) were observed and the C(6)-olefinated products were exclusively formed. The reaction of the OMe derivative **2a** without the S,O-ligand only gave a trace amount of olefinated product, highlighting the key role of the S,O-ligand in this transformation. We also evaluated the olefination reaction of substrate **5a** bearing a free OH group at the 5-position, but the olefinated product **5b** was obtained only in 27% yield due to its instability under the reaction conditions.[15] Having established the beneficial effect of the oxygenated moiety at the 5-position in the C−H olefination reaction, we decided to evaluate other protecting groups at the nitrogen atom. The reaction with the MOM-protected substrate **6a** provided the desired olefinated product **6b** in 46% yield with slightly lower C(6)-selectivity. When the benzyl-protected substrate **7a** was subjected to the standard reaction conditions, the olefinated product was obtained in 48% yield with good C(6)-selectivity.

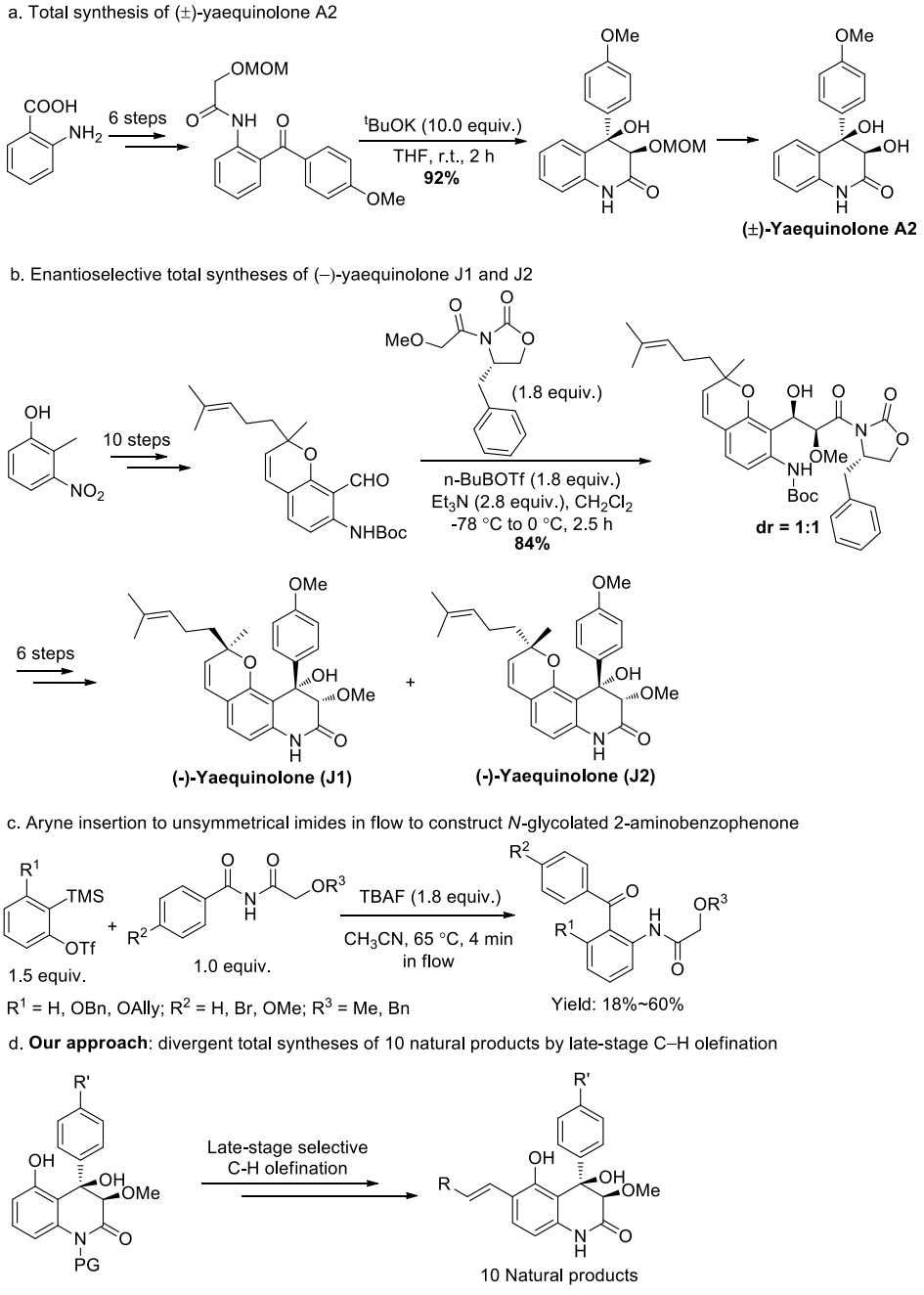
After having proved the suitability of the C−H olefination reaction on model substrates, we proposed the retrosynthetic route for 3,4-dioxygenated 4-aryl-5-hydroxy-quinolin-2(1*H*)-ones as outlined in Figure 2. 3,4-dioxygenated 4-aryl-5-hydroxy-quinolin-2(1*H*)-one can be obtained by cyclization as reported by the group of She.[8] The starting diarylketone can be synthesized from the nucleophilic addition of the lithiated 3-oxygenated 2-bromonitrobenzene, which can be prepared from commercially available 2-bromo-3-nitrophenol, to *para*-anisaldehyde, followed by oxidation.

The synthesis of the core structure is shown in Scheme 4. 2-Bromo-3-nitrophenol (**8**) was first protected with a benzyl group in 91% yield, followed by lithiation at low temperature and reaction with *para*-anisaldehyde, providing the corresponding alcohol **10** in 86% yield. We then reduced the nitro group using sodium sulfide to form the aniline intermediate **11**, followed by amide formation with methoxyacetyl chloride. The formed amide intermediate **12** was oxidized with PCC, providing the ketone **13** in 94% yield. The cyclization of **13** under reported reaction conditions produced (±)-**14** in 80% yield as a single diastereoisomer.[8] Then, we decided to protect the nitrogen atom with 2-(trimethylsilyl)ethoxymethyl (SEM), as it can be deprotected using mild reagents, such as tetrabutylammonium fluoride (TBAF).[16] Then, we introduced the SEM-protecting group to (±)-**14** using LiHMDS as the base. SEM-protected 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**16** was obtained in 95% yield after benzyl deprotection of (±)-**15** using Pd/C and H_2 (Scheme 4).

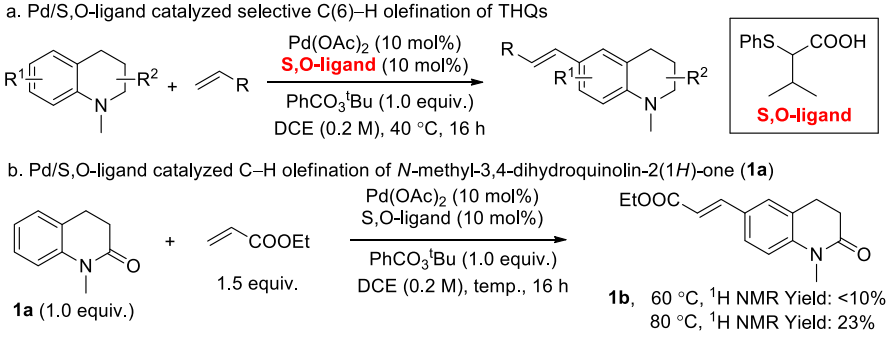
For the C−H olefination of (±)-**16**, we slightly optimized the reaction conditions and found that the best conditions were 2.0 equiv of $PhCO_3{}^tBu$ in dichloroethane (DCE) at 80 °C for 16 h, providing the olefinated product (±)-**17** in 59% isolated yield with a regioselectivity of 6:1 (A/B) together with 5% of the diolefinated product (Table 1). However, the regioisomers were not separable by flash column chromatography. We, therefore, continued the total synthesis with the mixture of regioisomers.

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

Scheme 1. Total Syntheses of Yaequinolone-Related Natural Products

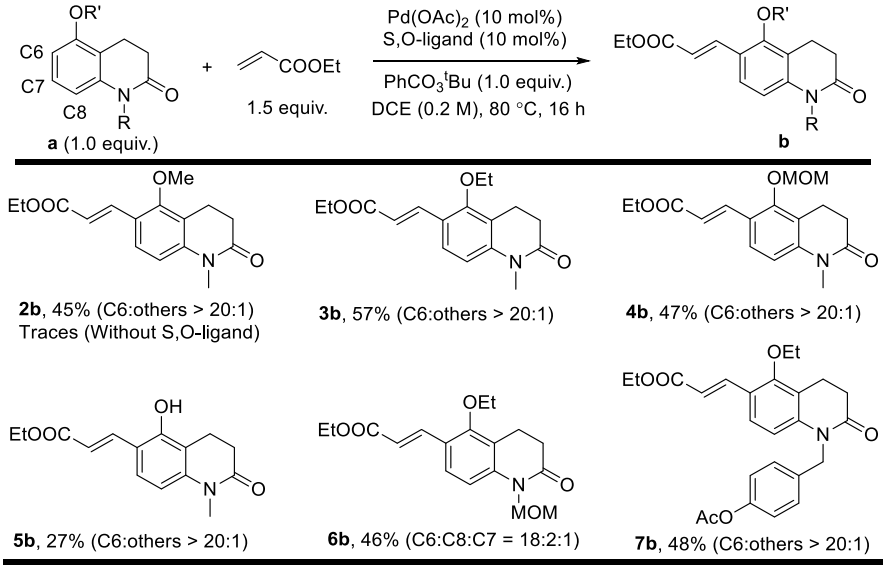


Scheme 2. Reactivity Comparison of THQs and 1a



https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259–6277

Scheme 3. C−H Olefination of 5-Oxgenated *N*-Methyl-3,4-dihydro-2(1*H*)-quinolinones[a,b,c]



[a]Reaction conditions: **a** (0.1 mmol), ethyl acrylate (0.15 mmol), $Pd(OAc)_2$ (0.01 mmol), S,O-ligand (0.01 mmol), and $PhCO_3{}^tBu$ (0.1 mmol) in DCE (0.5 mL) at 80 °C for 16 h. [b]Isolated yield. [c]Regioselectivity was determined based on the analysis of crude mixture.

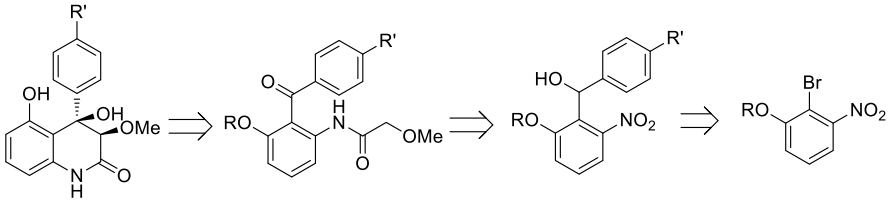


Figure 2. Retrosynthetic analysis of 3,4-dioxygenated 5-hydroxy-4-aryl-quinolin-2(1*H*)-ones.

We performed the deprotection of the SEM group with TBAF, and it was found out that a high concentration of TBAF is required to obtain the desired product in good yield. For instance, when the concentration of TBAF was 0.1 M, no product was observed even after refluxing the reaction for 20 h. When we increased the concentration to 1.0 M, to our delight, the reaction reached full conversion after refluxing for 15 h and (±)-yaequinolone B was obtained in 60% isolated yield as a single regioisomer (Scheme 5). Its ^1H and ^{13}C NMR data matched with those reported in the literature.[4c] Hence, the total synthesis of (±)-yaequinolone B was achieved in 10.6% overall yield in 10 synthetic steps starting from commercially available 2-bromo-3-nitrophenol.

Encouraged by these results, we moved our attention to the total syntheses of (±)-penigequinolones A and B, which can be accomplished by only changing the olefin coupling partner while keeping the same core structure (±)-**16**. Olefin (±)-**18** was prepared in six synthetic steps starting from ethyl isobutyrate (see the Experimental Section). The C−H olefination of (±)-**16** using (±)-**18** as the olefin under standard reaction conditions furnished the olefinated product (±)-**19** in 50% yield with a regioselectivity of 8.8:1 (A/B) and a diastereoselectivity of 1:1. The SEM deprotection of (±)-**19** with TBAF (4.0 M) almost quantitatively yielded a mixture of (±)-penigequinolones A and B (dr = 1:1) with improved regioselectivity (13.5:1) (Scheme 6). Their ^1H and ^{13}C NMR data matched with those reported in the literature.[4c]

For the synthesis of (±)-yaequinolone C, as the relative stereochemistry of the olefin moiety was not determined in the initial report from the group of Ōmura, we decided to first try the olefin (±)-***trans*-20** (see the Experimental Section).[4c] To our delight, the olefinated product (±)-**21** was isolated in 52% yield with a regioselectivity of 7:1 (A/B) (Scheme 7a). However, we observed the formation of four diastereoisomers, indicating that racemization of one of the stereocenters of the olefin moiety has occurred. To prove this, we performed the olefination of (±)-**16** with a mixture of (±)-***trans*-** and (±)-***cis*-20** (1:1), and we observed the formation of the same four diastereoisomers (Scheme 7b). Moreover, we further tried the olefination of the model substrate **5a** with (±)-***trans*-20** and with a 1:1 mixture of (±)-***trans*-** and (±)-***cis*-20** and in both cases, the olefinated product was obtained as a mixture of diastereoisomers in almost 1:1 ratio, confirming that racemization has occurred in one of the stereocenters of the olefin moiety during the C−H olefination (Scheme 7c).[17]

The deprotection of the olefinated product (±)-**21** (A/B = 7:1) using 4.0 M of TBAF reached full conversion after refluxing overnight, providing (±)-yaequinolone C together with three other diastereoisomers in 79% isolated yield with an improved regioselectivity of 10.4:1 (Scheme 8). Based on the results obtained from the reaction of (±)-**16** with (±)-***trans*-20** and with a 1:1 mixture of (±)-***trans*-** and (±)-***cis*-20**, we proposed that the olefin moiety has a trans-configuration (see Supporting Information). Therefore, the structure of (±)-yaequinolone C is either **22-A** or **22-B**.

In an effort to synthesize (±)-aspoquinolones C and D, we performed the olefination reaction of (±)-**16** with (±)-***cis*-23**, but no desired product was observed and (±)-**16** was fully

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

Scheme 4. Synthesis of the Core Structure (±)-16

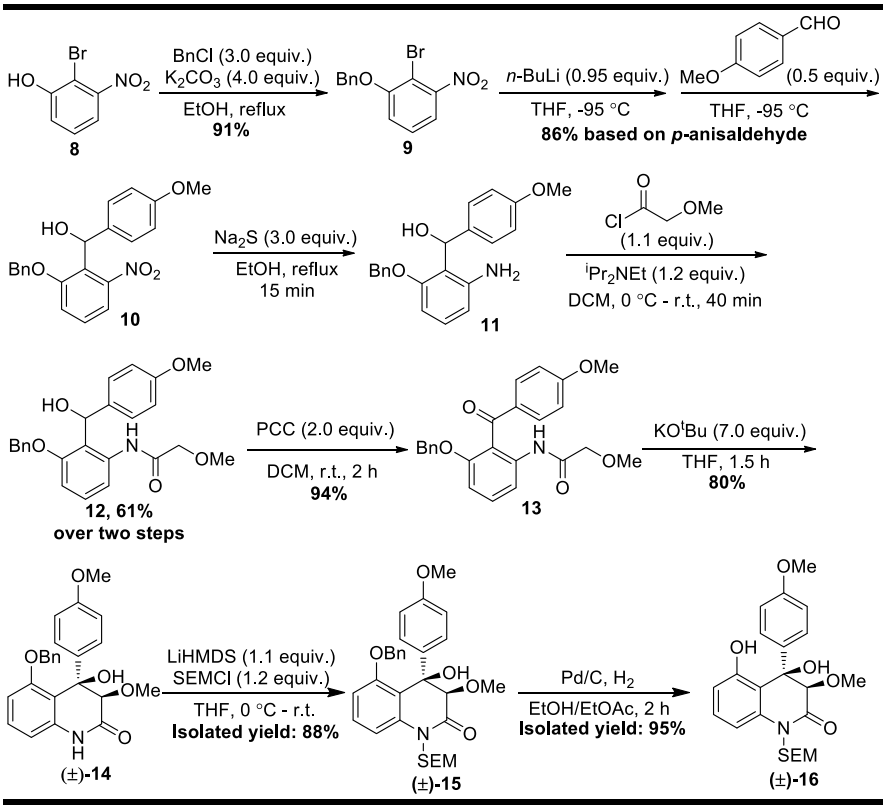
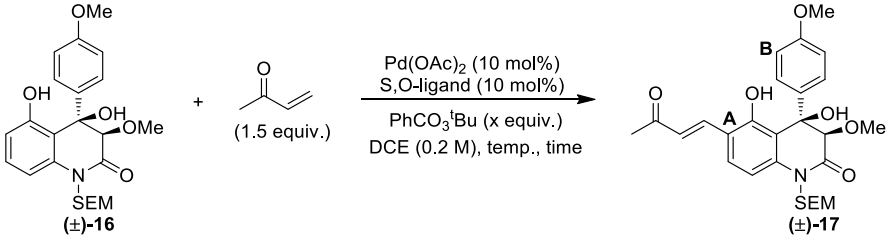


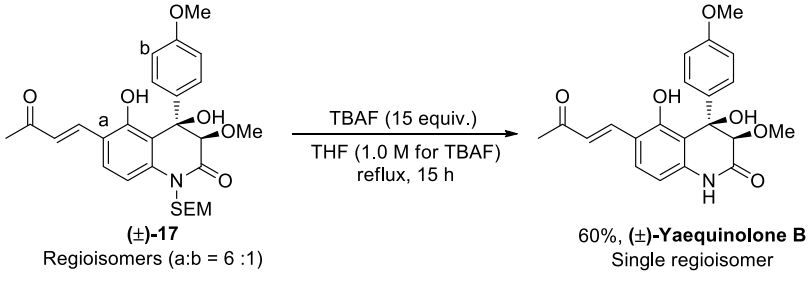
Table 1. Reaction Conditions for the C−H Olefination of (±)-16



entry	temp. (°C)	*x*	time (h)	^{1}H NMR yield[a]
1	80	1.5	16	49%
2	60	1.5	16	31%
3	80	1.5	6	45%
4	80	1.0	16	42%
5	**80**	**2.0**	**16**	54% (**59%**[b,c] + **5%**[b,d])
6[e]	80	1.5	16	55%

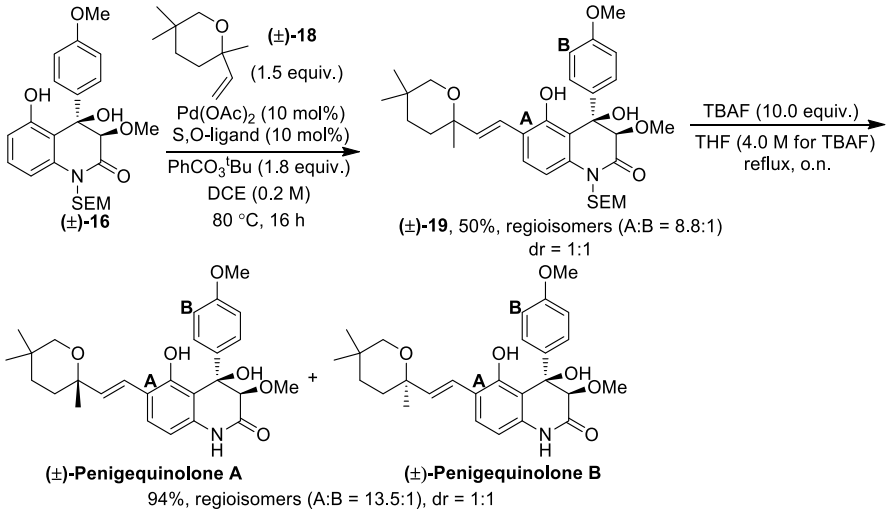
[a]^{1}H NMR yield of the desired regioisomer was determined by using CH_2Br_2 as the internal standard. [b]Isolated yield. [c]Regioselectivity was determined from the crude mixture: A/B = 6:1. [d]Diolefinated product. [e]15 mol % of $Pd(OAc)_2$ and S,O-ligand were used.

Scheme 5. Synthesis of (±)-Yaequinolone B

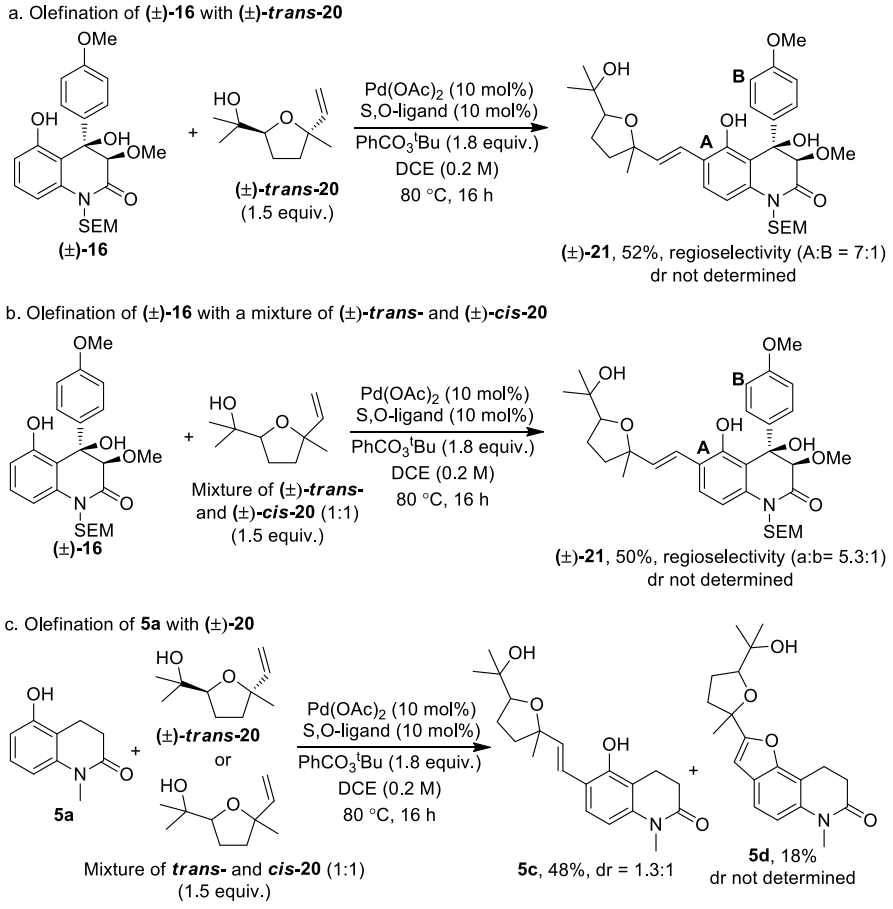


https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

Scheme 6. Syntheses of (±)-Penigequinolones A and B



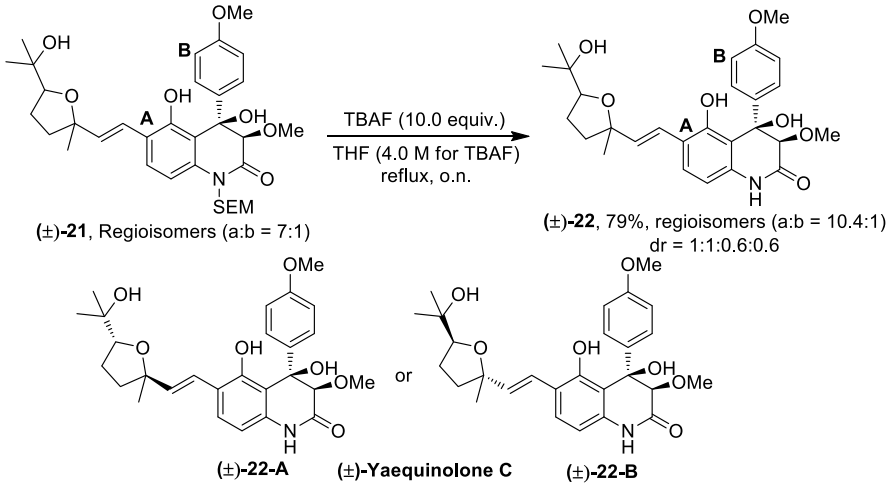
Scheme 7. C−H Olefination of (±)-16 and 5a with (±)-19



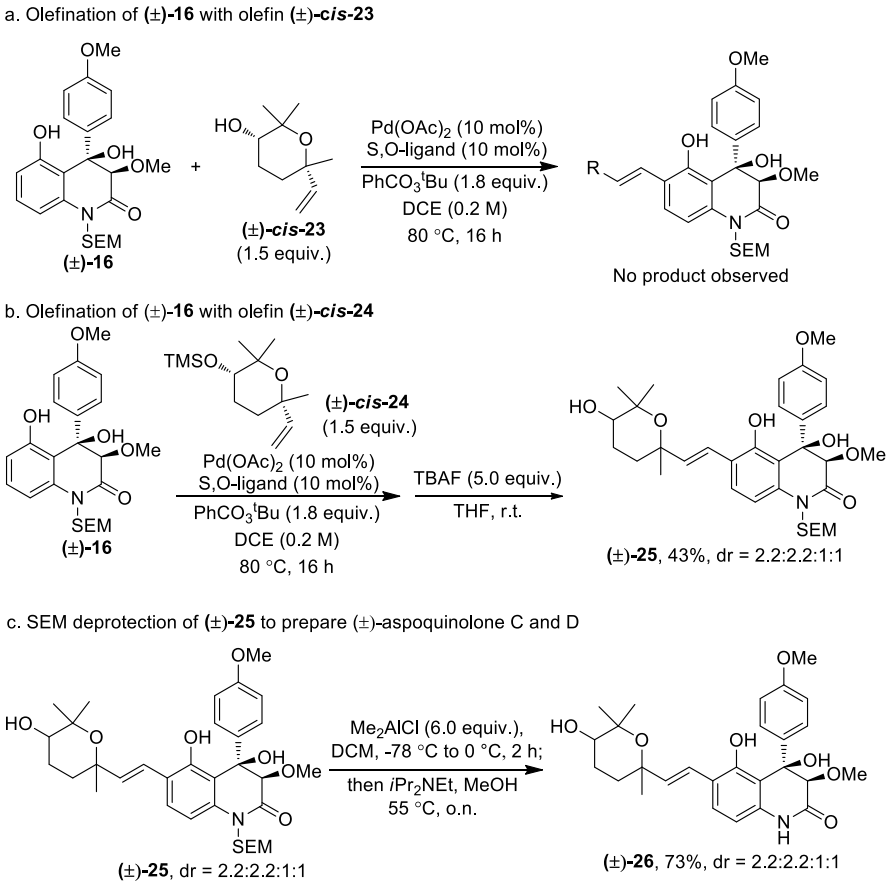
recovered (Scheme 9a). Considering that the free hydroxyl group from the olefin might be the problem, we protected the OH of (±)-*cis*-**23** with the TMS group. The reaction of (±)-**16** with TMS-protected olefin (±)-*cis*-**24** gave a mixture of TMS-protected and unprotected olefinated products with 50% conversion (Scheme 9b). To simplify the purification, we directly treated the crude mixture with TBAF to deprotect the TMS group.[18] After purification, the olefinated product (±)-**25** was isolated in 43% yield as a single regioisomer [the other regioisomer was detected by ^{1}H NMR analysis of the crude and separated by preparative thin layer chromatography (TLC)]. Unfortunately, like in the previous case, epimerization also occurred and four diastereoisomers were detected with a ratio of 2.2:2.2:1:1. The SEM deprotection of (±)-**25** with TBAF led to full decomposition of the starting material. Then, we performed the deprotection reaction using Me_2AlCl.[19] This two-step deprotection procedure provided (±)-aspoquinolones C and D together with two other

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

Scheme 8. Synthesis of (±)-Yaequinolone C



Scheme 9. Syntheses of (±)-Aspoquinolones C and D



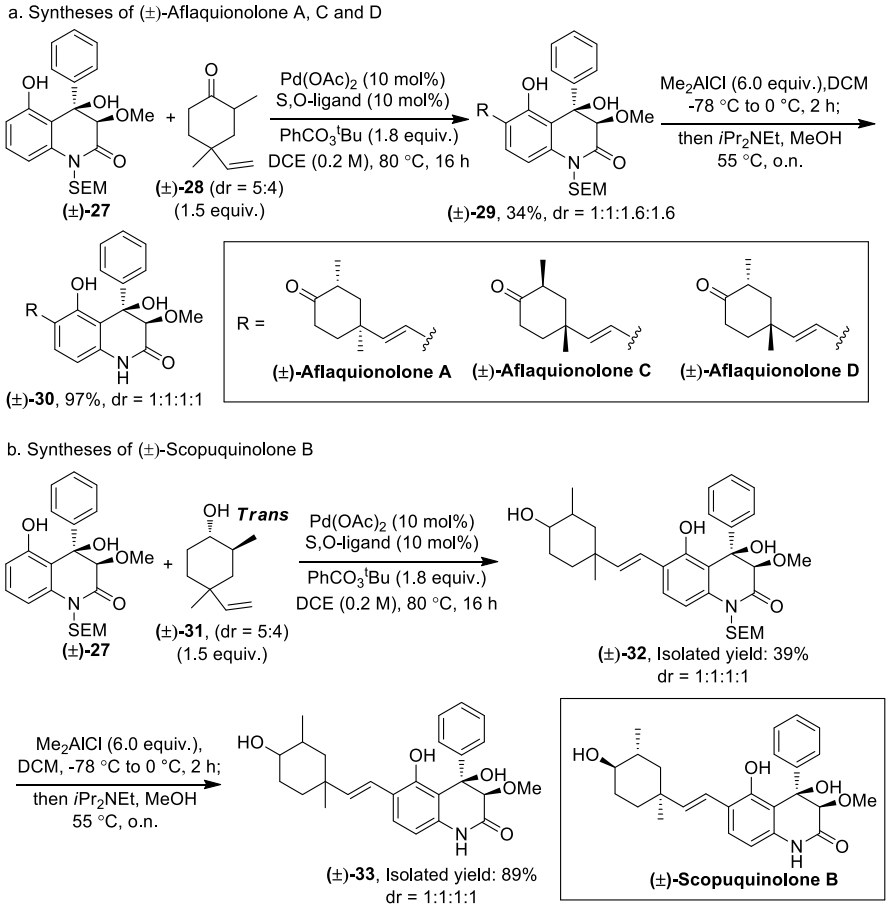
diastereoisomers with diastereoselectivity (2.2:2.2:1:1) remaining in 73% combined yield (Scheme 9c). As the relative stereochemistry of the olefin moieties of aspoquinolones C and D was not determined in the initial report,[4b] we propose, based on our results, that one has the cis-configuration on the olefin moiety and the other one has the trans-configuration.

After proving the synthetic power of late-stage C−H olefination by the Pd/S,O-ligand catalyst in the divergent synthesis of (±)-yaequinolones B and C, (±)-penigequinolones A and B, and (±)-aspoquinolones C and D, we decided to move our attention to the total syntheses of another class of closely related quinolone natural products, which all share a slightly different backbone (a phenyl group located at the 4-position instead of a 4-methoxyphenyl group). We prepared the corresponding 3,4-dihydro-2(1*H*)-quinolinone derivative (±)-**27** in seven synthetic steps starting from **9** using the same procedure for the preparation of (±)-**16** (see Experimental Section) (Scheme 10).

To synthesize (±)-aflaquinolones A, C, and D, we prepared olefin (±)-**28** as a mixture of diastereoisomers (trans/cis = 5:4) in seven synthetic steps starting from ethyl 4-oxocyclohexanecarboxylate (see the Experimental Section).[20]

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

Scheme 10. Syntheses of (±)-Aflaquinolones A, C, and D and (±)-Scopuquinolone B



The coupling of this unactivated olefin **28** with (±)-**27** gave the olefinated product (±)-**29** in 34% yield with perfect regioselectivity (>20:1) and with a diastereoselectivity of 1:1:1.6:1.6. The SEM deprotection of (±)-**29** with TBAF failed to give any desired product, while the reaction with Me_2AlCl provided (±)-aflaquinolones A, C, and D together with another diastereoisomer in near-quantitative yield with a diastereoselectivity of 1:1:1:1. Thus, epimerization occurred during the deprotection reaction probably at the α-position of the ketone.

Our last target was the synthesis of (±)-scopuquinolone B that can be synthesized by coupling the core structure (±)-**27** with the *trans*-olefin (±)-**31**. The olefination reaction of (±)-**27** with olefin (±)-**31** furnished the olefinated product (±)-**32** in 39% yield with a diastereoselectivity of 1:1:1:1. The SEM deprotection of (±)-**32** with Me_2AlCl provided (±)-scopuquinolone B together with three other diastereoisomers in 89% yield with retained diastereoselectivity of 1:1:1:1.

CONCLUSIONS

In summary, we have developed novel divergent syntheses of 10 yaequinolone-related natural products, which are synthesized for the first time, by late-stage C−H olefination of 3,4-dioxygenated 4-aryl-5-hydroxyquinolin-2(1*H*)-ones, core structures of this family of natural products. A robust synthetic methodology is established to construct the core structures and the C−H olefination reaction is efficient and site-selective under mild reaction conditions in the presence of a Pd/S,O-ligand catalyst. The power of the olefination reaction was showcased by successfully using unactivated olefins as coupling partners. Through this synthetic approach, the relative configuration of the olefin moiety of some of these natural products has been elucidated. Our future efforts will be devoted toward the divergent enantioselective total syntheses of this family of natural products.

EXPERIMENTAL SECTION

General Information. Chromatography: Silicycle Silica Flash P60 size 40−63 μm (230−400 mesh), TLC: Merck silica gel 60 (0.25 mm), and preparative TLC: Analtech silica gel G 1500 μm 20 × 20 cm. Visualization of the TLC plate was performed with phosphomolybdic acid or KMnO4 staining reagent and UV light. Mass spectra were recorded on AccuTOF GC v 4g, JMS-T100GCV mass spectrometers. ^{1}H and ^{13}C were recorded on Bruker 500 AMX, 400 and Bruker DRX 300 using $CDCl_3$ as the solvent otherwise it will be noted. Chemical shift values are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: δ 7.26 for ^{1}H and δ 77.16 for ^{13}C; dimethyl sulfoxide: δ 2.50 for ^{1}H and δ 39.52 for ^{13}C; and acetone: δ 2.05 for ^{1}H and δ 206.26 for ^{13}C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz), and integration. IR spectra were recorded on a Bruker Alpha Fourier transform infrared machine and wavelengths are reported in cm^{-1}. The melting point was measured in melting point apparatus Büchi M-565. Tetrahydrofuran (THF) and diethyl ether were dried over Na using benzophenone as the indicator. Dichloromethane was dried over CaH_2 and was used freshly after distillation. Anhydrous dimethylformamide (DMF) was purchased from Acros and used as received. Absolute ethanol was purchased

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

from VWR Amsterdam and was used as received. TBAF solution (1.0 M in THF) was purchased from Fluorochem And $Pd(OAc)_2$ was purchased from Strem. The S,O-ligand was prepared using the procedure reported in the literature.[13b]

Synthesis of Olefins. 2,5,5-Trimethyl-2-vinyltetrahydro-2*H*-pyran (**18**) was prepared using the following procedures: Step A: In a flame-dried Schlenk flask were added ethyl isobutyrate (5.563 mL, 4.84 g, 41.7 mmol, 1.0 equiv) and anhydrous THF (40 mL) under N_2. In another flask, lithium diisopropylamide (LDA) (50 mmol, 1.2 equiv) was prepared and transferred to the substrate flask at −78 °C via a cannula over a period of 0.5 h. The reaction was stirred for 2 h before 1-bromo-2-chloroethane (8.613 mL, 14.34 g, 100 mmol, 2.4 equiv) was added. The reaction was then warmed up to room temperature and stirred overnight. The reaction was quenched by adding saturated aqueous NH_4Cl solution and was extracted with EtOAc three times. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by flash column chromatography (PE/Et_2O, 100:1 to 50:1) giving ethyl 4-chloro-2,2-dimethylbutanoate (**Int-A**) as a colorless oil (6.10 g, 82%). Its ^1H NMR data matched with those reported in the literature.[21] ^1H NMR (400 MHz): δ 4.16 (q, J = 7.1 Hz, 2H), 3.57−3.48 (m, 2H), 2.12−2.03 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.24 (s, 6H).

Step B: In a flame-dried Schlenk flask were added $LiBH_4$ (0.92 g, 42 mmol, 1.5 equiv) and anhydrous DCM (20 mL). To this suspension was then slowly added MeOH (1.7 mL). After the evolution of H_2 has ceased, **Int-A** (5.00 g, 28 mmol, 1.0 equiv) was added. The reaction was then heated under reflux at 45 °C overnight. The reaction was quenched by carefully adding water and the mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by flash column chromatography (PE/Et_2O, 100:1 to 1:1) giving 4-chloro-2,2-dimethylbutan-1-ol (**Int-B**) as a colorless oil (2.50 g, 65%). Its ^1H NMR data matched with those reported in the literature.[22] ^1H NMR (300 MHz): δ 3.64−3.51 (m, 2H), 3.35 (d, J = 0.7 Hz, 2H), 1.88−1.75 (m, 2H), 0.93 (s, 6H).

Step C: In a round-bottom flask were successively added **Int-B** (1.37 g, 10 mmol, 1.0 equiv), DCM (15 mL), and TBSCl (3.01 g, 20 mmol, 2.0 equiv). After stirring the mixture for 5 min, 1-imidazole (1.36 g, 20 mmol, 2.0 equiv) was then added and the stirring was continued for another 2 h. Saturated aqueous NH_4Cl solution was added to quench the reaction and the mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by flash column chromatography (PE/Et_2O, 20:1) giving *tert*-butyl(4-chloro-2,2-dimethylbutoxy)dimethylsilane (**Int-C**) as a colorless oil (2.50 g, quantitative yield). ^1H NMR (300 MHz): δ 3.62−3.50 (m, 2H), 3.25 (s, 2H), 1.84−1.72 (m, 2H), 0.89 (s, 9H), 0.81 (s, 6H), 0.03 (s, 6H). $^{13}C\{H\}$ NMR (75 MHz): δ 71.7, 42.7, 41.8, 36.0, 26.0, 24.3, 18.4, −5.4. HRMS (FD) m/z: $[M - {}^tBu]^+$ calcd for $C_8H_{18}ClOSi^+$, 193.0815; found, 193.0854.

Step D: In a flame-dried Schlenk flask were added **Int-C** (1.50 g, 5.98 mmol, 1.0 equiv), Mg (0.18 g, 7.41 mmol, 1.24 equiv), and anhydrous THF (2 mL) under N_2. The mixture was then heated to reflux and a few drops of 1,2-dibromoethane were slowly added to the reaction. The reaction was continued to stir for another 6 h while refluxing at 80 °C. In another flame-dried Schlenk flask were added anhydrous $CeCl_3$ (1.47 g, 5.98 mmol, 1.0 equiv) and anhydrous THF (12 mL), and the suspension was stirred at room temperature for 1 h. The freshly prepared Grignard reagent was transferred to the suspension via a cannula at 0 °C. The reaction was further stirred at 0 °C for 1 h before but-3-en-2-one (1.0 mL, 11.96 mmol, 2.0 equiv) was added. After stirring it at 0 °C for 1 h, the reaction was quenched by adding saturated aqueous NH_4Cl solution and the mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by flash column chromatography (PE/EtOAc, 15:1) giving 7-[(*tert*-butyldimethylsilyl)oxy]-3,6,6-trimethylhept-1-en-3-ol (**Int-D**) as a colorless oil (1.01 g, 59%). ^1H NMR (400 MHz): δ 5.89 (dd, J = 17.4, 10.7 Hz, 1H), 5.20 (dd, J = 17.3, 1.4 Hz, 1H), 5.04 (dd, J = 10.8, 1.4 Hz, 1H), 3.22 (s, 2H), 1.51−1.46 (m, 2H), 1.27 (s, 3H), 1.25−1.20 (m, 2H), 0.89 (s, 9H), 0.02 (s, 6H). $^{13}C\{H\}$ NMR (75 MHz): δ 145.4, 111.8, 77.4, 73.5, 71.4, 36.5, 35.0, 32.5, 27.8, 26.1, 24.3, 24.3, 18.4, −5.4. HRMS (EI) m/z: $[M]^+$ calcd for $C_{16}H_{34}O_2Si^+$, 286.2328; found, 286.2295.

Step E: In a round-bottom flask were added **Int-D** (1.00 g, 3.49 mmol, 1.0 equiv) and THF (15 mL). TBAF solution (1.0 M in THF, 8.7 mL, 8.7 mmol, 2.5 equiv) was added dropwise. The reaction was left to stir at room temperature for 4 h before it was quenched by adding saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by flash column chromatography (*n*-hexane/EtOAc, 11:1) giving 2,2,5-trimethylhept-6-ene-1,5-diol (**Int-E**) as a white solid (0.50 g, 83%). ^1H NMR (300 MHz): δ 5.85 (dd, J = 17.3, 10.7 Hz, 1H), 5.16 (dd, J = 17.4, 1.3 Hz, 1H), 5.01 (dd, J = 10.8, 1.3 Hz, 1H), 3.33−3.18 (m, 2H), 2.76 (br s, 2H), 1.48−1.42 (m, 2H), 1.28−1.20 (m, 2H), 1.25 (s, 3H), 0.82 (s, 3H), 0.81 (s, 3H). $^{13}C\{H\}$ NMR (75 MHz): δ 145.2, 111.8, 73.4, 70.7, 35.9, 34.75, 31.6, 27.9, 24.5, 24.2. HRMS (FD) m/z: $[M]^+$ calcd for $C_{10}H_{20}O_2^+$, 172.1463; found, 172.1470.

Step F: In a flame-dried Schlenk flask were successively added **Int-E** (200 mg, 1.16 mmol, 1.0 equiv), DCE (25 mL), and anhydrous $ZnCl_2$ (158 mg, 1.16 mmol, 1.0 equiv) under N_2. The reaction was then stirred at 70 °C for 2 h before it was quenched by adding saturated aqueous NH_4Cl solution. The mixture was extracted with Et_2O three times. The combined extracts were passed through a short plug of silica gel and rinsed with Et_2O. The filtrate was evaporated in vacuo giving 2,5,5-trimethyl-2-vinyltetrahydro-2*H*-pyran (**18**) as a colorless oil (130 mg, 73%). ^1H NMR (400 MHz): δ 5.78 (dd, J = 17.4, 11.4 Hz, 1H), 5.17 (s, 1H), 5.13 (dd, J = 7.9, 1.3 Hz, 1H), 3.33 (d, J = 11.3 Hz, 1H), 3.21 (dd, J = 11.3, 2.0 Hz, 1H), 1.73−1.61 (m, 2H), 1.45−1.37 (m, 1H), 1.35−1.28 (m, 1H), 1.23 (s, 3H), 0.99 (s, 2H), 0.81 (s, 2H). $^{13}C\{H\}$ NMR (101 MHz): δ 143.3, 114.3, 74.2, 72.7, 33.5, 30.7, 29.8, 28.7, 26.7, 24.2. HRMS (FD) m/z: $[M + Na]^+$ calcd for $C_{10}H_{18}NaO^+$, 177.1255; found, 177.1268.

trans-Linalool oxide (***trans*-20**) was prepared using the following procedures: Linalool oxide was purchased from TCI as a mixture of diastereoisomers (1:1) not separable by flash column chromatography. To separate the diastereoisomers, the hydroxyl group was first protected with TMS using the following procedure:

In a round bottom flask were successively added linalool oxide (**20**, dr = 1:1) (1.01 g, 5.92 mmol, 1.0 equiv), DCM (12 mL), 1-imidazole (1.21 g, 17.8 mmol, 3.0 equiv), and TMSCl (1.13 mL, 8.88 mmol, 1.5 equiv). The reaction was then stirred at room temperature for 0.5 h before water was added. The mixture was extracted with Et_2O three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The product TMS-*trans*-linalool oxide (**TMS-*trans*-20**) was obtained as a colorless oil after purification by flash column chromatography using PE as the eluent. Its ^1H NMR data matched with those reported in the literature.[24] ^1H NMR (400 MHz): δ 5.86 (dd, J = 17.2, 10.5 Hz, 1H), 5.16 (d, J = 17.3 Hz, 1H), 4.97 (d, J = 10.6 Hz, 1H), 3.74 (t, J = 6.1 Hz, 1H), 1.94−1.76 (m, 3H), 1.71−1.63 (m, 1H), 1.30 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 0.11 (s, 9H).

The TMS-protecting group was then removed by using the following step: In a round bottom flask were added **TMS-*trans*-20** (2.70 g, 11.13 mmol, 1.0 equiv) and THF (50 mL). TBAF solution (33 mL, 1.0 M in THF, 3.0 equiv) was then added slowly. The reaction was stirred for 1 h before water was added. The mixture was extracted with Et_2O three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The sample was purified by flash column chromatography (*n*-hexane/EtOAc, 5:1) giving *trans*-linalool oxide (***trans*-20**) as a colorless oil (1.70 g, 89%). Its ^1H NMR data matched with those reported in the literature.[23] ^1H NMR (400 MHz): δ 5.88 (dd, J = 17.3, 10.6 Hz, 1H), 5.19 (d, J = 17.3 Hz, 1H), 5.00 (d, J = 10.7 Hz, 1H), 3.80 (t, J = 7.1 Hz, 1H), 2.10−1.79 (m, 5H), 1.78−1.67 (m, 1H), 1.32 (s, 3H), 1.23 (s, 3H), 1.14 (s, 3H).

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

*TMS-cis-2,2,6-trimethyl-6-vinyltetrahydropyran-3-ol (**cis-24**).* 2,2,6-Trimethyl-6-vinyltetrahydropyran-3-ol (**23**) was purchased from TCI as a mixture of diastereoisomers (1:1) not separable by flash column chromatography. The TMS protection and deprotection strategy was used to separate them as presented for the separation of linalool oxide (**20**). TMS protection was performed using the same procedure as the TMS protection of linalool oxide, and ***cis*-24** was isolated as a colorless oil after purification by flash column chromatography with PE as the eluent. ^{1}H NMR (400 MHz): δ 5.96 (ddd, J = 18.2, 10.9, 1.2 Hz, 1H), 4.99−4.91 (m, 2H), 3.40 (dd, J = 11.3, 4.1 Hz, 1H), 2.10 (dt, J = 12.7, 3.3 Hz, 1H), 1.80−1.65 (m, 1H), 1.62−1.48 (m, 2H), 1.15 (s, 3H), 1.14 (s, 3H), 1.13 (s, 3H), 0.10 (d, J = 1.1 Hz, 9H). ^{13}C{H} NMR (101 MHz): δ 146.6, 110.6, 76.6, 75.7, 73.5, 32.9, 32.2, 30.1, 26.4, 20.9, 0.05. HRMS (FD) m/z: $[M - Me]^+$ calcd for $C_{12}H_{23}O_2Si^+$, 227.1467; found, 227.1485.

*cis-2,2,6-Trimethyl-6-vinyltetrahydropyran-3-ol (**cis-23**).* Deprotection of ***cis*-24** (0.60 g, 2.475 mmol) was performed using the same procedure as the deprotection of TMS-*trans*-linalool oxide (**TMS-*trans*-20**). ***cis*-23** was isolated as a wax (0.42 g, quantitative yield) and its ^{1}H NMR data matched with those reported in the literature.[24] ^{1}H NMR (400 MHz): δ 5.99 (dd, J = 18.1, 11.0 Hz, 1H), 5.03 (d, J = 5.5 Hz, 1H), 4.99 (d, J = 1.1 Hz, 1H), 3.51−3.43 (m, 1H), 2.15 (dt, J = 13.6, 3.7 Hz, 1H), 1.77−1.71 (m, 2H), 1.64−1.58 (m, 1H), 1.28 (s, 3H), 1.20 (s, 3H), 1.19 (s, 3H).

2,4-Dimethyl-4-vinylcyclohexanone (**28**) and 2,4-dimethyl-4-vinylcyclohexanol (**31**) were prepared using the following procedures: Step A: In a round-bottom flask were successively added ethyl 4-oxocyclohexane-1-carboxylate (9.29 mL, 10.00 g, 58.8 mmol, 1.0 equiv), ethylene glycol (11.5 mL, 12.77 g, 205.8 mmol, 3.5 equiv), *p*-toluenesulfonic acid monohydrate (137 mg, 0.012 equiv), and anhydrous toluene (30 mL). The reaction was then stirred overnight at room temperature. Saturated aqueous Na_2CO_3 solution was added and the reaction was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by flash column chromatography (PE/EtOAc, 15:1) giving ethyl 1,4-dioxaspiro[4.5]decane-8-carboxylate as a colorless oil (10.94 g, 87%). Its ^{1}H NMR data matched with those reported in the literature.[25] ^{1}H NMR (400 MHz): δ 4.05 (q, J = 7.1 Hz, 2H), 3.86 (s, 4H), 2.29−2.22 (m, 1H), 1.91−1.80 (m, 2H), 1.79−1.64 (m, 4H), 1.54−1.42 (m, 2H), 1.17 (t, J = 7.1 Hz, 3H).

Step B: In a flame-dried Schlenk flask were successively added 1,4-dioxaspiro[4.5]decane-8-carboxylate (10.94 g, 51.1 mmol, 1.0 equiv) and anhydrous THF (70 mL). The solution was slowly transferred to another Schlenk flask containing freshly prepared LDA (66.4 mmol, 1.3 equiv) at −78 °C over a period of 0.5 h. THF (10 mL) was used to rinse the flask and was also transferred. The reaction was then slowly warmed up to room temperature and stirred for 0.5 h before it was cooled to −78 °C again. MeI (6.36 mL, 14.50 g, 102.2 mmol, 2.0 equiv) was added dropwise and the reaction was slowly warmed up to room temperature. After stirring it overnight, the reaction was quenched by adding saturated aqueous NH_4Cl solution and was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by flash column chromatography (PE/EtOAc, 20:1) giving ethyl 8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate as a colorless oil (9.68 g, 83%). Its ^{1}H NMR data matched with those reported in the literature.[25] ^{1}H NMR (400 MHz): δ 4.02 (q, J = 7.1 Hz, 2H), 3.81 (s, 4H), 2.00 (dt, J = 13.0, 3.6 Hz, 2H), 1.58−1.32 (m, 6H), δ 1.13 (t, J = 7.1 Hz, 3H), 1.06 (s, 3H).

Step C: In a flame-dried Schlenk flask were added ethyl 8-methyl-1,4-dioxaspiro[4.5]decane-8-carboxylate (7.20 g, 31.5 mmol, 1.0 equiv) and anhydrous DCM (70 mL). LAH (2.63 g, 69.4 mmol, 2.2 equiv) was added in small portions at 0 °C. The reaction was stirred at 0 °C for 0.5 h before it was warmed up to room temperature slowly. After the reaction was stirred for 1.5 h, the reaction was diluted with DCM and saturated aqueous potassium sodium tartrate solution was carefully added. The reaction was then stirred vigorously for 1 h. The mixture was extracted with DCM three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo to give (8-methyl-1,4-dioxaspiro[4.5]decan-8-yl)methanol as a white solid (5.81 g, 99%), which was pure enough to continue for the next step without further purification. Its ^{1}H NMR data matched with those reported in the literature.[25] ^{1}H NMR (400 MHz): δ 3.94 (d, J = 1.7 Hz, 4H), 3.39 (s, 2H), 1.73−1.49 (m, 6H), 1.45−1.34 (m, 3H), 0.96 (s, 3H).

Step D: In a round-bottom flask were successively added (8-methyl-1,4-dioxaspiro[4.5]decan-8-yl)methanol (4.90 g, 26.3 mmol, 1.0 equiv), DCM (60 mL), and PCC (12.48 g, 57.9 mmol, 2.2 equiv). After the reaction was stirred at room temperature for 1 h, it was filtrated through a plug of silica gel and rinsed with EtOAc. The filtrate was evaporated and purified by flash column chromatography (PE/EtOAc, 5:1) giving 8-methyl-1,4-dioxaspiro[4.5]decane-8-carbaldehyde a colorless oil (4.20 g, 87%). Its ^{1}H NMR data matched with those reported in the literature.[26] ^{1}H NMR (400 MHz): δ 9.46 (s, 1H), 3.93 (s, 4H), 2.07−1.92 (m, 2H), 1.70−1.49 (m, 6H), 1.04 (s, 3H).

Step E: In a flame-dried Schlenk flask were added methyl triphenylphosphonium bromide (13.44 g, 37.6 mmol, 1.65 equiv) and anhydrous THF (75 mL) at 0 °C under N_2. *n*-BuLi (13.7 mL, 2.5 M in hexanes, 34.25 mmol, 1.5 equiv) was then added dropwise. The reaction was warmed up to room temperature and stirred for 0.5 h before it was cooled to 0 °C again. In another flask, a solution of 8-methyl-1,4-dioxaspiro[4.5]decane-8-carbaldehyde (4.20 g, 22.8 mmol, 1.0 equiv) in anhydrous THF (20 mL) was prepared and the solution was slowly transferred to the Wittig reagent flask via a cannula over a period of 0.5 h. 10 mL of anhydrous THF was used to rinse the flask and was also transferred. The reaction was then stirred at room temperature for 3 h. Acetone (5 mL) was added to quench the Wittig reagent. The mixture was filtrated and washed with Et_2O. The filtrate was evaporated and purified by flash column chromatography (*n*-pentane/Et_2O, 15:1) giving 8-methyl-8-vinyl-1,4-dioxaspiro[4.5]-decane as a pale yellow oil (3.46 g, 83%). Its ^{1}H NMR data matched with those reported in the literature.[26] ^{1}H NMR (400 MHz): δ 5.79 (dd, J = 17.8, 10.7 Hz, 1H), 5.01 (d, J = 4.6 Hz, 1H), 4.98 (s, 1H), 3.93 (s, 4H), 1.69−1.61 (m, 6H), 1.53−1.44 (m, 2H), 1.01 (s, 3H).

Step F: 8-Methyl-8-vinyl-1,4-dioxaspiro[4.5]decane (3.40 g, 18.7 mmol) was dissolved in acetone (60 mL). 10% HCl (24 mL) was then added dropwise. The reaction was stirred for 2.5 h before brine was added. The mixture was extracted with DCM/Et_2O (1:2) three times. The volatiles were carefully evaporated in vacuo giving 4-methyl-4-vinylcyclohexan-1-one as a colorless oil (2.57 g, quantitative yield). Its ^{1}H NMR data matched with those reported in the literature.[26] ^{1}H NMR (400 MHz): δ 5.89 (dd, J = 17.5, 11.0 Hz, 1H), 5.18−5.08 (m, 2H), 2.45−2.25 (m, 4H), 1.97−1.90 (m, 2H), 1.74−1.67 (m, 2H), 1.12 (d, J = 0.9 Hz, 3H).

Step G: In a flame-dried Schlenk flask was added LiHMDS (7.6 mL, 1.0 M in THF, 7.6 mmol, 1.05 equiv) under N_2 and 4-methyl-4-vinylcyclohexan-1-one (1.00 g, 7.2 mmol, 1.0 equiv) in DMF (4 mL) was added dropwise at −78 °C. The reaction was then left to stir for 1.5 h before MeI (446 μL, 7.2 mmol, 1.0 equiv) was added dropwise. The reaction was slowly warmed up to room temperature and stirred overnight. The reaction was quenched by adding saturated aqueous NH_4Cl solution and was extracted with Et_2O three times. The combined extracts were washed with water three times and brine, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by flash column chromatography (*n*-pentane/Et_2O, 20:1) giving 2,4-dimethyl-4-vinylcyclohexan-1-one (**28**) as a pale yellow oil (0.82 g, 74%, dr: trans/cis = 5:4). ^{1}H NMR (400 MHz): δ 5.98 (dd, J = 17.6, 10.9 Hz, $1H_{trans}$), 5.84 (dd, J = 17.5, 10.7 Hz, $1H_{cis}$), 5.26−5.19 (m, $1H_{trans}$ and $1H_{cis}$), 5.04−4.95 (m, $1H_{trans}$ and $1H_{cis}$), 2.66−2.41 (m, $2H_{trans}$ and $2H_{cis}$), 2.34 (dt, J = 14.4, 3.8 Hz, $1H_{cis}$), 2.25 (ddd, J = 14.0, 4.5, 2.5 Hz, $1H_{trans}$), 2.10−2.01 (m, $1H_{trans}$ and $1H_{cis}$), 1.81−1.77 (m, $1H_{trans}$), 1.73−1.65 (m, $1H_{cis}$), 1.51 (t, J = 13.4 Hz, $1H_{cis}$), 1.44 (m, t, J = 13.4 Hz, $1H_{trans}$), 1.33 (s, $3H_{cis}$), 1.06 (s, $3H_{trans}$), 1.04 (d, J = 6.5 Hz, $2H_{cis}$), 1.01 (d, J = 6.5 Hz, $3H_{trans}$). ^{13}C{H} NMR (75 MHz): δ 213.9, 213.5, 148.3, 144.8, 113.5, 110.6, 47.0, 46.4, 41.3, 40.7, 38.5 (trans and cis), 37.9 (trans and cis), 37.7, 37.5, 30.3, 22.1, 14.7, 14.5. HRMS (FD) m/z: $[M]^+$ calcd for $C_{10}H_{16}O^+$, 152.1201; found, 152.1211.

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

Step H: In a flame-dried Schlenk flask were added **37** (dr = 5:4, 0.36 g, 2.36 mmol, 1.0 equiv) and anhydrous Et_2O (70 mL). LAH (0.18 g, 4.74 mmol, 2.0 equiv) was added in small portions at 0 °C. The reaction was stirred for 0.5 h before it was warmed up to room temperature slowly. After the reaction was stirred for 1.5 h, the reaction was diluted with Et_2O and saturated aqueous potassium sodium tartrate solution was carefully added. The reaction was then stirred vigorously for 1 h. The mixture was extracted with Et_2O three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by flash column chromatography (*n*-pentane/Et_2O, 5:1) giving 2,4-dimethyl-4-vinylcyclohexanol (**31**) as a pale yellow oil (0.35 g, 96%, dr: A/B = 5:4). ^{1}H NMR (300 MHz): δ 5.78 (dd, J = 17.6, 10.8 Hz, $1H_A$ and $1H_B$), 5.07−4.84 (m, $2H_A$ and $2H_B$), 3.14−3.05 (m, $1H_A$ and $1H_B$), 1.87−1.22 (m, $7H_A$ and $7H_B$), 1.05 (s, $3H_B$), 0.99 (d, J = 6.5 Hz, $3H_B$), 0.97 (d, J = 6.7 Hz, $3H_A$), 0.95 (s, $3H_A$). ^{13}C{H} NMR (75 MHz): δ 150.4, 146.2, 112.5, 109.4, 45.4, 44.4, 37.2, 36.5, 36.4, 36.1, 35.5, 35.5, 31.9 (A and B), 31.2, 31.1, 22.4 (A and B), 18.8, 18.7. HRMS (FD) m/z: $[M]^+$ calcd for $C_{10}H_{18}O^+$, 154.1358; found, 154.1360.

Synthesis of Model Substrates. *5-Methoxy-N-methyl-3,4-dihydroquinolin-2(1H)-one (**2a**).* In a flame-dried Schlenk flask were added 5-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (326 mg, 2.0 mmol, 1.0 equiv) and anhydrous DMF (10 mL) under N_2. NaH (240 mg, 60% in mineral oil, 6.0 mmol, 3.0 equiv) was then added at 0 °C and stirred for 0.5 h. MeI (500 μL, 8.0 mmol, 4.0 equiv) was then added dropwise at 0 °C. The reaction was then warmed up to room temperature and stirred overnight. The reaction was quenched by adding water and extracted with EtOAc three times. The combined organic extracts were washed with water three times and brine two times, dried with Na_2SO_4, filtrated, and concentrated in vacuo to give **2a** as a pale yellow solid (380 mg, 99%). Its ^{1}H NMR data matched with those reported in the literature.[27] ^{1}H NMR (400 MHz): δ 7.21 (t, J = 8.2 Hz, 1H), 6.64 (d, J = 8.3 Hz, 2H), 3.85 (s, 3H), 3.35 (s, 3H), 2.89 (dd, J = 8.6, 6.4 Hz, 2H), 2.60 (dd, J = 8.6, 6.4 Hz, 2H).

*5-Hydroxy-N-methyl-3,4-dihydroquinolin-2(1H)-one (**5a**).* In a flame-dried Schlenk flask were added **2a** (1.15 g, 6.0 mmol, 1.0 equiv) and anhydrous DCM (10 mL) under N_2. A solution of BBr_3 in DCM (18 mL, 1.0 M, 18.0 mmol, 3.0 equiv) was added dropwise at −78 °C. After stirring the reaction for another 1 h at −78 °C, the reaction was slowly warmed up to room temperature and stirred for additional 3 h. Water was slowly added to quench the reaction and the reaction was extracted with DCM three times. The combined organic extracts were washed with water and brine, dried with $MgSO_4$, filtrated, and concentrated in vacuo to give **5a** as a pale yellow solid (1.02 g, 96%). Its ^{1}H NMR data matched with those reported in the literature.[28] ^{1}H NMR (400 MHz): δ 7.11 (t, J = 8.2 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 6.54 (d, J = 7.9 Hz, 1H), 3.35 (s, 3H), 2.90 (dd, J = 8.7, 6.3 Hz, 2H), 2.64 (dd, J = 8.5, 6.4 Hz, 2H).

*5-(Methoxymethoxy)-N-methyl-3,4-dihydroquinolin-2(1H)-one (**4a**).* In a flame-dried Schlenk flask were added **5a** (532 mg, 3.0 mmol, 1.0 equiv) and freshly distilled THF (10 mL) under N_2. NaH (156 mg, 60% in mineral oil, 3.9 mmol, 1.3 equiv) was then added portionwise at 0 °C. After stirring it at room temperature for 0.5 h, MOMCl (1.127 g, 15.1 mmol, 1.2 equiv) was added to the reaction dropwise at 0 °C. After stirring it for 3 h at room temperature, the reaction was quenched by slowly adding water and extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by flash column chromatography (*n*-hexane/EtOAc, 3:1) giving **4a** as a pale yellow solid (500 mg, 75%). ^{1}H NMR (400 MHz): δ 7.18 (t, J = 8.3 Hz, 1H), 6.85 (dd, J = 8.4, 0.9 Hz, 1H), 6.68 (d, J = 8.2 Hz, 1H), 5.21 (s, 2H), 3.49 (s, 3H), 3.35 (s, 3H), 2.93 (dd, J = 8.6, 6.4 Hz, 2H), 2.61 (dd, J = 8.6, 6.4 Hz, 2H). ^{13}C{H} NMR (75 MHz): δ 170.6, 154.1, 141.9, 127.8, 115.5, 109.3, 108.8, 94.8, 56.3, 31.2, 29.9, 18.3. HRMS (FD) m/z: $[M]^+$ calcd for $C_{12}H_{15}NO_3^+$, 221.1052; found, 221.1061.

5-Ethoxy-3,4-dihydroquinolin-2(1H)-one. In a flame-dried Schlenk flask were added 5-hydroxy-3,4-dihydroquinolin-2(1*H*)-one (0.70 g, 4.29 mmol, 1.0 equiv), K_2CO_3 (1.23 mg, 8.93 mmol, 2.1 equiv), EtBr (0.7 mg, 6.42 mmol, 1.5 equiv), and anhydrous DMF (5 mL) under N_2. The reaction was then stirred at 70 °C for 5 h. Water was then added and the mixture was extracted with EtOAc three times. The combined organic extracts were washed with water three times and brine two times, dried with $MgSO_4$, filtrated, and concentrated in vacuo to yield 5-ethoxy-3,4-dihydroquinolin-2(1*H*)-one as a white solid (800 mg, 98%), which was pure enough to be directly used for the next step. Its ^{1}H NMR data matched with those reported in the literature.[29] ^{1}H NMR (400 MHz): δ 7.58 (br s, 1H), 7.10 (t, J = 8.1 Hz, 1H), 6.56 (d, J = 8.2 Hz, 1H), 6.35 (d, J = 7.9 Hz, 1H), 4.05 (q, J = 7.0 Hz, 2H), 2.97 (t, J = 7.7 Hz, 2H), 2.60 (dd, J = 8.4, 6.9 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H).

*5-Ethoxy-N-methyl-3,4-dihydroquinolin-2(1H)-one (**3a**).* In a flame-dried Schlenk flask were added 5-ethoxy-3,4-dihydroquinolin-2(1*H*)-one (191 mg, 1.0 mmol, 1.0 equiv) and anhydrous DMF (2 mL) under N_2. NaH (60 mg, 60% in mineral oil, 1.5 mmol, 1.5 equiv) was then added at 0 °C and stirred for 0.5 h. MeI (170 mg, 1.2 mmol, 1.2 equiv) was then added dropwise at 0 °C. The reaction was then warmed up to room temperature and stirred overnight. The reaction was quenched by adding water and extracted with EtOAc three times. The combined organic extracts were washed with water three times and brine two times, dried with $MgSO_4$, filtrated, and concentrated in vacuo to give **3a** as a white solid (200 mg, 98%). Its ^{1}H NMR data matched with those reported in the literature.[29] ^{1}H NMR (400 MHz): δ 7.20−7.15 (m, 1H), 6.63−6.61 (m, 2H), 4.05 (q, J = 7.0 Hz, 2H), 3.34 (s, 3H), 2.93−2.88 (m, 2H), 2.60 (t, J = 7.3 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H).

*5-Ethoxy-N-(methoxymethyl)-3,4-dihydroquinolin-2(1H)-one (**6a**).* In a flame-dried Schlenk flask were added 5-ethoxy-3,4-dihydroquinolin-2(1*H*)-one (150 mg, 0.78 mmol, 1.0 equiv) and freshly distilled THF (3 mL) under N_2. NaH (47 mg, 60% in mineral oil, 1.17 mmol, 1.5 equiv) was then added at 0 °C. After stirring it for 0.5 h at 0 °C, MOMCl (70 μL, 0.94 mmol, 1.2 equiv) was added to the reaction at 0 °C dropwise. After stirring it for 2 h at room temperature, the reaction was quenched by slowly adding water and extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by flash column chromatography (PE/EtOAc, 4:1) giving **6a** as a pale yellow solid (99 mg, 54%). ^{1}H NMR (300 MHz): δ 7.21−7.12 (m, 1H), 6.93 (d, J = 7.9 Hz, 1H), 6.63 (d, J = 8.2 Hz, 1H), 5.30 (s, 2H), 4.05 (q, J = 6.5 Hz, 2H), 3.40 (s, 3H), 2.93 (t, J = 7.5 Hz, 2H), 2.68−2.62 (m, 2H), 1.42 (t, J = 7.0 Hz, 3H). ^{13}C{H} NMR (101 MHz): δ 171.7, 155.7, 140.9, 127.9, 114.7, 108.8, 107.1, 74.2, 64.1, 56.4, 31.5, 18.3, 15.0. HRMS (FD) m/z: $[M]^+$ calcd for $C_{13}H_{17}NO_3^+$, 235.1208; found, 235.1219.

*4-{[5-Ethoxy-2-oxo-3,4-dihydroquinolin-1(2H)-yl]methyl}phenyl Acetate (**7a**).* In a flame-dried Schlenk flask were added 5-ethoxy-3,4-dihydroquinolin-2(1*H*)-one (215 mg, 1.12 mmol, 1.0 equiv) and anhydrous DMF (3 mL) under N_2. NaH (54 mg, 60% in mineral oil, 1.35 mmol, 1.2 equiv) was then added at 0 °C and stirred for 0.5 h at 0 °C. 4-(Bromomethyl)phenyl acetate (332 mg, 1.46 mmol, 1.3 equiv) was then added at 0 °C. The reaction was then warmed up to room temperature and stirred overnight. The reaction was quenched by adding water and extracted with EtOAc three times. The combined organic extracts were washed with water three times and brine two times, dried over MgSO4, filtrated, and concentrated in vacuo. The product was purified by flash column chromatography (*n*-hexane/EtOAc, 3:1) giving **7a** as a pale yellow solid (250 mg, 66%). mp 102.0−103.3 °C. ^{1}H NMR (400 MHz): δ 7.22 (d, J = 8.2 Hz, 2H), 7.07−7.01 (m, 3H), 6.58 (d, J = 8.3 Hz, 1H), 6.51 (d, J = 8.2 Hz, 1H), 5.15 (s, 2H), 4.04 (q, J = 6.9 Hz, 2H), 2.98 (dd, J = 8.6, 6.3 Hz, 2H), 2.73 (dd, J = 8.7, 6.3 Hz, 2H), 2.27 (s, 3H), 1.42 (t, J = 6.9, 3H). ^{13}C{H} NMR (101 MHz): δ 170.8, 169.6, 155.9, 149.7, 141.0, 135.0, 127.8, 127.6, 121.9, 114.8, 108.5, 106.8, 64.1, 46.0, 31.5, 21.3, 18.3, 15.0. IR ν: 2977, 1758, 1671, 1594, 1467, 1188, 728 cm^{-1}. HRMS (FD) m/z: $[M]^+$ calcd for $C_{20}H_{21}NO_4^+$, 339.1471; found, 339.1471.

Synthesis of Core Structures (±)-16 and (±)-27 of Yaequinolone-Related Natural Products. *Synthesis of (±)-16. 1-(Benzyloxy)-2-bromo-3-nitrobenzene (**9**).* In a round-bottom flask were added 2-bromo-3-nitrophenol (**8**) (2.18 g, 10.0 mmol, 1.0

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

equiv), K_2CO_3 (4.15 g, 30.0 mmol, 3.0 equiv), benzyl chloride (2.3 mL, 20 mmol, 2.0 equiv), and EtOH (15 mL) successively. The mixture was then refluxed at 85 °C overnight. The volatiles were removed in vacuo. The product was purified by flash column chromatography (PE/EtOAc, 3:1) giving **9** as a yellow solid (2.80 g, 91%). mp 73.0−74.0 °C. ^{1}H NMR (400 MHz): δ 7.49 (d, J = 7.6 Hz, 2H), 7.48−7.26 (m, 5H), 7.17−7.09 (m, 1H), 5.25 (s, 2H). ^{13}C{H} NMR (101 MHz): δ 156.6, 135.6, 128.9, 128.7, 128.5, 127.2, 117.0, 116.4, 105.5, 71.8. HRMS (FD) m/z: $[M]^+$ calcd for $C_{13}H_{10}BrNO_3^+$, 306.9844; found, 306.9816.

*[2-(Benzyloxy)-6-nitrophenyl](4-methoxyphenyl)methanol (**10**).* In a flame-dried Schlenk flask were added **9** (4.00 g, 13.0 mmol, 1.0 equiv) and freshly distilled THF (50 mL) under N_2. At −95 °C, *n*-BuLi (6.24 mL, 2.5 M in hexanes, 15.6 mmol, 1.2 equiv) was then added dropwise. The reaction was continued to stir at −95 °C for 1.5 h before a solution of *p*-anisaldehyde (3.54 g, 26.0 mmol, 2.0 equiv) in THF (10 mL) was added dropwise. After stirring the reaction for another 2 h, the reaction was quenched by slow addition of saturated solution of NH_4Cl and extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The sample was purified by flash column chromatography (*n*-hexane/EtOAc, 5:1 to 3:1) giving **10** as a pale yellow oil (2.20 g, 46%). Another reaction using 4.00 g of **9** (13.0 mmol) with 0.95 equiv of *n*-BuLi and 0.5 equiv of *para*-anisaldehyde was also performed, and 2.06 g of **10** was obtained (86% based on *p*ara-anisaldehyde). ^{1}H NMR (400 MHz): δ 7.44−7.36 (m, 2H), 7.31−7.27 (m, 3H), 7.24−7.18 (m, 3H), 7.02 (dd, J = 7.5, 2.1 Hz, 2H), 6.86−6.82 (m, 2H), 6.23 (d, J = 10.5 Hz, 1H), 5.07 (d, J = 11.5 Hz, 1H), 4.99 (d, J = 11.5 Hz, 1H), 3.81 (s, 3H). ^{13}C{H} NMR (101 MHz): δ 158.8, 157.1, 150.7, 135.1, 134.6, 129.2, 128.6, 128.4, 127.5, 127.1, 126.4, 116.6, 116.5, 113.5, 71.2, 69.4, 55.3. IR ν: 3545, 2934, 1604, 1509, 1356, 1246, 1025, 737 cm^{-1}. HRMS (FD) m/z: $[M]^+$ calcd for $C_{21}H_{19}NO_5^+$, 365.1263; found, 365.1248.

*[2-Amino-6-(benzyloxy)phenyl](4-methoxyphenyl)methanol (**11**).* In a round bottom flask were added **10** (2.00 g, 5.5 mmol, 1.0 equiv), EtOH (30 mL), and Na_2S (1.28 g, 16.4 mmol, 3.0 equiv) successively. The reaction was then refluxed at 85 °C for 15 min before water was added to quench the reaction. The mixture was then extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The obtained **11** was directly used for the next step. ^{1}H NMR (400 MHz): δ 7.38−7.30 (m, 8H), 7.04 (t, J = 8.1 Hz, 1H), 6.87−6.82 (m, 2H), 6.49 (s, 1H), 6.45 (dd, J = 8.3, 1.0 Hz, 1H), 6.32 (dd, J = 8.0, 0.9 Hz, 1H), 5.08 (d, J = 11.7 Hz, 1H), 5.02 (d, J = 11.7 Hz, 1H), 3.78 (s, 3H). ^{13}C NMR (101 MHz): δ 158.7, 156.9, 146.4, 137.1, 135.0, 129.1, 128.6, 128.0, 127.5, 127.2, 116.6, 113.7, 111.1, 102.7, 70.6, 68.4, 55.4.

*N-{3-(Benzyloxy)-2-[hydroxy(4-methoxyphenyl)methyl]phenyl}-2-methoxyacetamide (**12**).* In a flame-dried Schlenk flask were added crude **11** obtained from the previous step, ^{i}Pr$_2$NEt (853 mg, 6.6 mmol, 1.2 equiv), and freshly distilled DCM (25 mL). 2-Methoxyacetyl chloride (657 mg, 6.05 mmol, 1.1 equiv) was then added dropwise at 0 °C. The reaction was stirred for another 40 min at room temperature before it was quenched by adding water. The reaction was extracted with DCM three times and the combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The product was purified by flash column chromatography (*n*-hexane/EtOAc, 2:1) giving **12** as a pale yellow oil (1.40 g, 61% over two steps). ^{1}H NMR (400 MHz): δ 10.09 (br s, 1H), 7.95 (d, J = 8.3 Hz, 1H), 7.38−7.22 (m, 8H), 6.82−6.78 (m, 3H), 6.65 (s, 1H), 5.11 (d, J = 11.7 Hz, 1H), 5.04 (d, J = 11.7 Hz, 1H), 3.87 (d, J = 15.4 Hz, 1H), 3.77 (s, 3H), 3.69 (d, J = 15.5 Hz, 1H), 3.28 (s, 3H). ^{13}C{H} NMR (101 MHz): δ 168.2, 158.3, 155.4, 137.6, 136.6, 134.4, 128.5, 128.3, 127.7, 127.1, 127.0, 121.1, 115.2, 113.2, 108.0, 72.0, 70.3, 67.4, 59.1, 54.9. IR ν: 3282, 2934, 2834, 1665, 1593, 1472, 1249, 1116 cm^{-1}. HRMS (FD) m/z: $[M]^+$ calcd for $C_{24}H_{25}NO_5^+$, 407.1733; found, 407.1746.

*N-[3-(Benzyloxy)-2-(4-methoxybenzoyl)phenyl]-2-methoxyacetamide (**13**).* In a round bottom flask were added **12** (1.40 g, 3.44 mmo, 1.0 equiv) and DCM (30 mL). PCC (1.48 g, 6.88 mmol, 2.0 equiv) was then added portionwise. After stirring it at room temperature for 1 h, TLC showed full conversion of the reaction. The reaction was then quenched by a saturated solution of Na_2SO_3 and extracted with DCM three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by flash column chromatography (*n*-hexane/EtOAc, 1.5:1) giving **13** as a pale yellow oil (1.30 g, 94%). ^{1}H NMR (400 MHz): δ 9.32 (br s, 1H), 7.99 (d, J = 8.3 Hz, 1H), 7.82−7.75 (m, 2H), 7.37 (t, J = 8.4 Hz, 1H), 7.19−7.06 (m, 3H), 6.91−6.82 (m, 4H), 6.78 (d, J = 8.3 Hz, 1H), 4.89 (s, 2H), 3.87 (s, 2H), 3.78 (s, 3H), 3.32 (s, 3H). ^{13}C{H} NMR (101 MHz): δ 194.9, 168.1, 163.7, 156.6, 136.3, 136.0, 131.7, 131.5, 128.0, 127.4, 126.5, 119.1, 114.8, 113.5, 108.3, 71.9, 70.0, 59.2, 55.3. IR ν: 3359, 2935, 2837, 1692, 1592, 1461, 1253, 927 cm^{-1}. HRMS (FD) m/z: $[M]^+$ calcd for $C_{24}H_{23}NO_5^+$, 405.1576; found, 405.1591.

(3R,4R*)-5-(Benzyloxy)-4-hydroxy-3-methoxy-4-(4-methoxyphenyl)-3,4-dihydroquinolin-2(1H)-one [(±)-**14**].* In a flame-dried Schlenk flask were added **13** (0.94 g, 2.32 mmol, 1.0 equiv) and freshly distilled THF (50 mL) at 0 °C under N_2. A solution of KO^{t}Bu (16.2 mL, 1.0 M in THF, 16.2 mmol, 7.0 equiv) was then added dropwise. After stirring it at 0 °C for 2 h, TLC showed full conversion of the reaction. The reaction was quenched by adding water and extracted with EtOAc (three times). The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by flash column chromatography (*n*-hexane/EtOAc, 1:1.5) giving (±)-**14** as a single diastereoisomer: white solid (0.75 g, 80%). ^{1}H NMR (400 MHz): δ 8.80 (br s, 1H), 7.32−7.25 (m, 3H), 7.25−7.16 (m, 3H), 7.12 (dd, J = 6.3, 2.7 Hz, 2H), 6.86−6.77 (m, 2H), 6.73 (d, J = 8.4 Hz, 1H), 6.55 (dd, J = 8.1, 0.9 Hz, 1H), 5.33 (s, 1H), 5.07 (d, J = 11.5 Hz, 1H), 4.99 (d, J = 11.5 Hz, 1H), 3.83 (s, 1H), 3.77 (d, J = 1.0 Hz, 3H), 3.61 (s, 3H). ^{13}C{H} NMR (101 MHz): δ 168.3, 159.7, 158.0, 137.1, 135.7, 133.6, 129.9, 128.7, 128.4, 127.6, 127.5, 115.3, 114.0, 109.6, 108.7, 85.1, 78.1, 71.1, 59.7, 55.3. IR ν: 3509, 2932, 1692, 1607, 1509, 1259, 1103 cm^{-1}. HRMS (FD) m/z: $[M]^+$ calcd for $C_{24}H_{23}NO_5^+$, 405.1576; found, 405.1591.

(3R,4R*)-5-(Benzyloxy)-4-hydroxy-3-methoxy-4-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1H)-one [(±)-**15**].* In a flame-dried Schlenk flask were added (±)-**14** (1.20 g, 2.96 mmol, 1.0 equiv) and anhydrous THF (50 mL) under N_2. LiHMDS solution in THF (3.26 mL, 1.0 M, 3.26 mmol, 1.1 equiv) was then added dropwise at 0 °C. After stirring it for 0.5 h, SEMCl (0.59 g, 3.55 mmol, 1.2 equiv) was added dropwise. The reaction was continued to stir at 0 °C for 2 h before water was added to quench the reaction. The mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The product was purified by flash column chromatography (PE/EtOAc, 3:1) giving (±)-**15** as a white solid (1.40 g, 88%). ^{1}H NMR (400 MHz): δ 7.33 (t, J = 8.3 Hz, 1H), 7.30−7.26 (m, 3H), 7.19−7.11 (m, 5H), 6.84−6.80 (m, 3H), 5.67 (d, J = 11.0 Hz, 1H), 5.49 (s, 1H), 5.10 (d, J = 11.5 Hz, 1H), 5.01 (d, J = 11.5 Hz, 1H), 4.96 (d, J = 11.0 Hz, 1H), 3.92 (s, 1H), 3.78 (s, 3H), 3.67−3.54 (m, 2H), 3.58 (s, 3H), 0.98−0.94 (m, 2H), 0.00 (s, 9H). ^{13}C{H} NMR (101 MHz): δ 167.6, 159.8, 157.4, 139.8, 135.7, 133.5, 129.7, 128.8, 128.4, 127.7, 127.5, 116.9, 114.0, 110.0, 109.3, 85.3, 77.4, 72.2, 71.2, 66.0, 59.4, 55.3, 18.1, −1.3. IR ν: 3508, 2952, 1693, 1594, 1465, 1385, 1247, 1064, 832 cm^{-1}. HRMS (FD) m/z: $[M]^+$ calcd for $C_{30}H_{37}NO_6Si^+$, 535.2390; found, 535.2383.

(3R,4R*)-4,5-Dihydroxy-3-methoxy-4-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1H)-one [(±)-**16**].* In a Schlenk flask were added (±)-**15** (430 mg), EtOH (5 mL), EtOAc (5 mL), and Pd/C (100 mg, 10 wt %) under N_2. The flask atmosphere was then changed to H_2 by using a balloon filled with H_2. The reaction was then stirred for 2 h under H_2 (1 atm. pressure). The reaction was filtrated and evaporated in vacuo. The product was purified by flash column chromatography (*n*-hexane/EtOAc, 3:1) giving (±)-**17** as a white solid (446 mg, 95%). 430 mg of (±)-**15** (0.80 mmol) and 100 mg Pd/C (10% wt) were used. Purification was performed using PE/EtOAc (3:1) as an eluent. Product (±)-**16** was isolated as a white solid in 95% yield (340 mg).

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

^{1}H NMR (400 MHz): δ 8.86 (s, 1H), 7.28 (t, J = 8.2 Hz, 1H), 7.17−7.15 (m, 2H), 6.98 (d, J = 8.3 Hz, 1H), 6.85−6.82 (m, 2H), 6.74 (d, J = 8.3 Hz, 1H), 5.65 (d, J = 11.0 Hz, 1H), 5.00 (d, J = 10.9 Hz, 1H), 4.53 (s, 1H), 3.85 (s, 1H), 3.77 (s, 3H), 3.63−3.53 (m, 2H), 3.59 (s, 3H), 0.96 (t, J = 8.3 Hz, 2H), 0.00 (s, 9H). ^{13}C{H} NMR (101 MHz): δ 166.1, 160.4, 157.6, 138.1, 130.4, 129.0, 128.2, 114.3, 113.8, 112.3, 107.7, 84.6, 78.1, 72.2, 66.1, 58.8, 55.3, 18.1, −1.3. IR ν: 3353, 2953, 1677, 1613, 1470, 1243, 1073, 834 cm^{-1}. HRMS (FD) m/z: [M]$^+$ calcd for $C_{23}H_{31}NO_6Si^+$, 445.1921; found, 445.1939.

Synthesis of (±)-27. [2-(Benzyloxy)-6-nitrophenyl](phenyl)-methanol (Int-F). The procedure for the preparation of **10** was followed. 4.00 g of **9** (13.0 mmol) was used and purification was performed using PE/EtOAc (7:1 to 3:1) as an eluent. Product **Int-F** was isolated as a yellow oil in 48% yield (2.10 g). Another reaction using 4.00 g of **9** (13.0 mmol) with 0.95 equiv of *n*-BuLi and 0.5 equiv of anisaldehyde was also performed, and 1.93 g of **Int-F** was obtained (88% based on anisaldehyde). ^{1}H NMR (400 MHz): δ 7.41−7.36 (m, 2H), 7.34−7.20 (m, 8H), 7.15 (d, J = 7.9 Hz, 1H), 6.94−6.87 (m, 2H), 6.26 (s, 1H), 5.02 (dd, J = 11.6, 2.8 Hz, 1H), 4.92 (d, J = 11.5 Hz, 1H). ^{13}C{H} NMR (101 MHz): δ 157.3, 151.0, 142.6, 135.0, 129.4, 128.8, 128.6, 128.3, 127.6, 127.3, 126.6, 125.8, 116.8, 77.4, 71.5, 69.6. IR ν: 3031, 1528, 1452, 1356, 1023, 737, 697 cm^{-1}. HRMS (EI) m/z: [M − OH]$^+$ calcd for $C_{20}H_{16}NO_3^+$, 318.1130; found, 318.1110.

[2-Amino-6-(benzyloxy)phenyl](phenyl)methanol (Int-G). The procedure for the preparation of **11** was followed. 1.80 g of **Int-F** (5.4 mmol) was used and the reaction was refluxed for 0.5 h. Product **Int-G** was used for the next step without purification. ^{1}H NMR (400 MHz): δ 7.46 (d, J = 7.5 Hz, 2H), 7.42−7.16 (m, 8H), 7.08 (t, J = 8.2 Hz, 1H), 6.57 (s, 1H), 6.49 (d, J = 8.3 Hz, 1H), 6.35 (d, J = 7.9 Hz, 1H), 5.17−5.02 (m, 2H). ^{13}C{H} NMR (101 MHz): δ 156.9, 146.1, 143.0, 137.1, 129.2, 128.6, 128.3, 128.0, 127.5, 127.0, 125.9, 116.7, 111.2, 102.9, 70.6, 68.5.

N-{3-(Benzyloxy)-2-[hydroxy(phenyl)methyl]phenyl}-2-methoxyacetamide (Int-H). The procedure for the preparation of **12** was followed. The crude sample **Int-G** from the previous step was used and purification was performed using PE/EtOAc (2.5:1) as an eluent. Product **Int-H** was isolated as a yellow oil in 67% yield (2.10 g) over two steps. ^{1}H NMR (400 MHz): δ 9.76 (s, 1H), 7.89 (d, J = 8.3 Hz, 1H), 7.41−7.16 (m, 11H), 6.82 (d, J = 8.4 Hz, 1H), 6.67 (s, 1H), 5.13 (d, J = 11.6 Hz, 1H), 5.05 (d, J = 11.6 Hz, 1H), 3.89 (d, J = 15.4 Hz, 1H), 3.67 (d, J = 15.3 Hz, 1H), 3.29 (s, 3H). ^{13}C{H} NMR (101 MHz): δ 168.3, 156.0, 142.0, 137.7, 136.7, 129.3, 128.7, 128.2, 128.2, 127.6, 127.2, 125.8, 121.4, 116.1, 108.7, 72.4, 71.0, 68.2, 59.5. IR ν: 3293, 2934, 1665, 1592, 1443, 1261, 1117, 736 cm^{-1}. HRMS (EI) m/z: [M − H_2O]$^+$ calcd for $C_{23}H_{21}NO_3^+$, 359.1521; found, 359.1513.

N-[2-Benzoyl-3-(benzyloxy)phenyl]-2-methoxyacetamide (Int-I). The procedure for the preparation of **13** was followed. 1.46 g of **Int-H** (3.87 mmol) was used and purification was performed using PE/EtOAc (2:1) as eluent. Product **Int-I** was isolated as a pale yellow solid in 89% yield (1.29 g). ^{1}H NMR (400 MHz): δ 9.53 (s, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H), 7.59−7.50 (m, 3H), 7.46−7.40 (m, 3H), 7.20−7.11 (m, 3H), 6.81 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 7.6 Hz, 2H), 4.88 (d, J = 2.0 Hz, 2H), 3.92 (d, J = 1.9 Hz, 2H), 3.39 (d, J = 2.3 Hz, 3H). ^{13}C{H} NMR (101 MHz): δ 197.0, 168.4, 157.3, 139.3, 137.0, 135.9, 133.0, 132.4, 129.2, 128.4, 128.2, 127.7, 126.7, 118.6, 115.0, 108.4, 72.2, 70.3, 59.5. IR ν: 3354, 2936, 1692, 1581, 1466, 1274, 1070, 923, 697 cm^{-1}. HRMS (EI) m/z: [M]$^+$ calcd for $C_{23}H_{21}NO_4^+$, 375.1471; found, 375.1464.

(3R,4R*)-5-(Benzyloxy)-4-hydroxy-3-methoxy-4-phenyl-3,4-dihydroquinolin-2(1H)-one [(±)-Int-J].* The procedure for the preparation of (±)-**14** was followed. 1.15 g of **Int-I** (3.06 mmol) was used and purification was performed using PE/EtOAc (1:1) as an eluent. Product (±)-**Int-J** was isolated as a white solid in 95% yield (1.10 g). ^{1}H NMR (400 MHz): δ 8.76 (br s, 1H), 7.27−7.18 (m, 9H), 7.06−7.03 (m, 2H), 6.70 (d, J = 8.3 Hz, 1H), 6.55 (d, J = 8.3 Hz, 1H), 5.28 (br s, 1H), 5.03 (d, J = 11.6 Hz, 1H), 4.93 (d, J = 11.6 Hz, 1H), 3.83 (s, 1H), 3.59 (s, 3H). ^{13}C{H} NMR (101 MHz): δ 168.1, 158.0, 141.9, 137.2, 135.7, 130.0, 128.7, 128.7, 128.4, 128.3, 127.4, 126.2, 115.2, 109.6, 108.7, 85.0, 78.3, 71.0, 59.8. Its NMR data matched with those reported in the literature.[10a]

(3R,4R*)-5-(Benzyloxy)-4-hydroxy-3-methoxy-4-phenyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1H)-one [(±)-Int-K].* In a flame-dried Schlenk flask were added (±)-**Int-J** (0.90 g, 2.40 mmol, 1.0 equiv) and anhydrous THF (35 mL). LiHMDS solution in THF (3.12 mL, 1.0 M, 3.12 mmol, 1.3 equiv) was then added dropwise at 0 °C. After stirring it for 0.5 h, SEMCl (0.60 g, 3.60 mmol, 1.5 equiv) was added dropwise. The reaction was first stirred at 0 °C for 0.5 h and then 2 h at room temperature. Water was added to quench the reaction. The mixture was extracted with EtOAc three times. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The sample was purified by flash column chromatography (PE/EtOAc, 4:1) giving (±)-**Int-K** as a white solid (1.15 g, 94%). ^{1}H NMR (400 MHz): δ 7.31 (t, J = 8.3 Hz, 1H), 7.29−7.20 (m, 8H), 7.16 (d, J = 8.4 Hz, 1H), 7.08−6.99 (m, 2H), 6.80 (d, J = 8.4 Hz, 1H), 5.64 (d, J = 11.0 Hz, 1H), 5.47 (br s, 1H), 5.05 (d, J = 11.5 Hz, 1H), 4.97−4.94 (m, 2H), 3.91 (s, 1H), 3.66−3.53 (m, 2H), 3.56 (s, 3H), 0.98−0.93 (m, 2H), −0.02 (s, 9H). ^{13}C{H} NMR (101 MHz): δ 167.5, 157.4, 141.7, 139.9, 135.7, 129.8, 128.7, 128.6, 128.5, 128.3, 127.4, 126.3, 116.7, 109.9, 109.2, 85.2, 77.6, 72.2, 71.2, 66.0, 59.5, 18.1, −1.3. IR ν: 3507, 2951, 1693, 1593, 1469, 1376, 1247, 1062, 833, 730, 696 cm^{-1}. HRMS (FD) m/z: [M]$^+$ calcd for $C_{29}H_{35}NO_5Si^+$, 505.2284; found, 505.2302.

(3R,4R*)-4,5-Dihydroxy-3-methoxy-4-phenyl-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1H)-one [(±)-27].* The procedure for the preparation of (±)-**16** was followed. 0.90 g of (±)-**Int-K** (2.17 mmol) was used and purification was performed using PE/EtOAc (4:1) as an eluent. Product (±)-**27** was isolated as a white solid in 94% yield (0.70 g). ^{1}H NMR (400 MHz): δ 8.80 (br s, 1H), 7.32−7.29 (m, 3H), 7.28−7.20 (m, 3H), 6.98 (d, J = 8.2 Hz, 1H), 6.72 (d, J = 8.3 Hz, 1H), 5.65 (d, J = 10.9 Hz, 1H), 5.00 (d, J = 10.9 Hz, 1H), 4.54 (s, 1H), 3.82 (s, 1H), 3.60−3.54 (m, 2H), 3.58 (s, 3H), 0.97−0.92 (m, 2H), −0.02 (s, 9H). ^{13}C{H} NMR (101 MHz): δ 165.9, 157.6, 138.3, 137.3, 130.6, 129.5, 129.0, 126.7, 113.9, 112.2, 107.8, 84.6, 78.3, 72.3, 66.2, 58.9, 18.1, −1.3. IR ν: 3325, 2952, 1680, 1470, 1241, 1070, 834 cm^{-1}. HRMS (FD) m/z: [M]$^+$ calcd for $C_{22}H_{29}NO_5Si^+$, 415.1815; found, 415.1836.

C(6)−H Olefination of 3,4-Dihydro-2(1*H*)-quinolinone Derivatives. *General Procedure.* In a pressure tube containing a suitable stirring bar were added the corresponding 3,4-dihydro-2(1*H*)-quinolinone derivative (1.0 equiv), $Pd(OAc)_2$ (10 mol %), $PhCO_3^tBu$ (1.0−2.0 equiv), olefin (1.5 equiv), S,O-ligand stock solution in DCE (0.1 M, 10 mol %), and DCE. The tube was introduced into an oil bath preheated at 80 °C and was stirred for 16 h. The tube was then removed from the oil bath and cooled to room temperature. The reaction was filtrated through Celite and rinsed with DCM. The filtrate was then washed with a saturated solution of Na_2CO_3, dried with $MgSO_4$, filtrated, and concentrated in vacuo. The product was purified by flash column chromatography.

(E)-Ethyl 3-(1-Methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)-acrylate (1b). Substrate **1a** (16.1 mg, 0.1 mmol) was olefinated using ethyl acrylate (16.3 μL, 0.15 mmol, 1.5 equiv) and $PhCO_3^tBu$ (18.6 μL, 0.1 mmol, 1.0 equiv) for 16 h following the general procedure, and the sample was purified by preparative TLC (PE/EtOAc, 5:1) to give **1b** as a yellow oil (9.0 mg, 35%) as a mixture of regioisomers (para/others 4.3:1). ^{1}H NMR (400 MHz): δ 7.63 (d, J = 16.1 Hz, 1H), 7.42 (dd, J = 8.4, 2.1 Hz, 1H), 7.35 (d, J = 1.9 Hz, 1H), 6.98 (d, J = 8.4 Hz, 1H), 6.37 (d, J = 16.0 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.37 (s, 3H), 2.93 (dd, J = 8.6, 6.1 Hz, 2H), 2.68 (dd, J = 8.7, 6.0 Hz, 3H), 1.34 (t, J = 7.1 Hz, 4H). HRMS (FD) m/z: [M]$^+$ calcd for $C_{15}H_{17}NO_3^+$, 259.1208; found, 259.1184.

(E)-Ethyl 3-(5-Methoxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)acrylate (2b). Substrate **2a** (19.1 mg, 0.1 mmol) was olefinated using ethyl acrylate (16.3 μL, 0.15 mmol, 1.5 equiv) and $PhCO_3^tBu$ (18.6 μL, 0.1 mmol, 1.0 equiv) following the general procedure, and the sample was purified by flash column chromatography (PE/EtOAc, 3:1) to give **2b** as a yellow oil (13.0 mg, 45%, C6/others > 20:1). ^{1}H NMR (400 MHz): δ 7.88 (d, J = 16.1 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 6.80 (d, J = 8.6 Hz, 1H), 6.45

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

(d, J = 16.1 Hz, 1H), 4.27 (q, J = 7.1 Hz, 2H), 3.74 (s, 3H), 3.36 (s, 3H), 2.97 (dd, J = 8.6, 6.3 Hz, 2H), 2.63 (dd, J = 8.6, 6.2 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C{H} NMR (101 MHz): δ 170.3, 167.4, 156.7, 143.7, 139.0, 127.2, 123.1, 120.1, 118.3, 111.4, 62.0, 60.6, 31.1, 29.9, 18.8, 14.5. IR ν: 2923, 2852, 1675, 1628, 1596, 1265, 1167 cm^{-1}. HRMS (FD) m/z: [M]$^+$ calcd for $C_{16}H_{19}NO_4^+$, 289.1314; found, 289.1319. A parallel reaction was performed without using the S,O-ligand and only a trace amount of desired product was detected.

*(E)-Ethyl 3-(5-Ethoxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)acrylate (**3b**).* Substrate **3a** (20.5 mg, 0.1 mmol) was olefinated using ethyl acrylate (16.3 μL, 0.15 mmol, 1.5 equiv) and PhCO$_3^t$Bu (18.6 μL, 0.1 mmol, 1.0 equiv) following the general procedure, and the sample was purified by flash column chromatography (PE/EtOAc, 3:1) to give **3b** as a yellow oil (17.3 mg, 57%, C6/others > 20:1). ^{1}H NMR (400 MHz): δ 7.90 (d, J = 16.1 Hz, 1H), 7.47 (d, J = 8.6 Hz, 1H), 6.79 (d, J = 8.6 Hz, 1H), 6.42 (d, J = 16.1 Hz, 1H), 4.25 (q, J = 7.1 Hz, 2H), 3.86 (q, J = 7.0 Hz, 2H), 3.35 (s, 3H), 2.95 (dd, J = 8.6, 6.2 Hz, 2H), 2.61 (dd, J = 8.5, 6.2 Hz, 2H), 1.42 (t, J = 7.0 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C{H} NMR (101 MHz): δ 170.3, 167.3, 155.7, 143.7, 139.3, 126.8, 123.3, 120.3, 118.0, 111.3, 70.7, 60.5, 31.2, 29.9, 19.0, 15.6, 14.5. IR ν: 2977, 1679, 1598, 1441, 1352, 1177, 1125, 1044 cm^{-1}. HRMS (FD) m/z: [M]$^+$ calcd for $C_{17}H_{21}NO_4^+$, 303.1471; found, 303.1488.

*(E)-Ethyl 3-[5-(Methoxymethoxy)-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]acrylate (**4b**).* Substrate **4a** (22.1 mg, 0.1 mmol) was olefinated using ethyl acrylate (16.3 μL, 0.15 mmol, 1.5 equiv) and PhCO$_3^t$Bu (18.6 μL, 0.1 mmol, 1.0 equiv) following the general procedure, and the sample was purified by flash column chromatography (PE/EtOAc, 3:1) to give **4b** as a yellow oil (15.0 mg, 47%, C6/others > 20:1). ^{1}H NMR (400 MHz): δ 7.93 (d, J = 16.1 Hz, 1H), 7.50 (d, J = 8.5 Hz, 1H), 6.82 (d, J = 8.6 Hz, 1H), 6.38 (d, J = 16.2 Hz, 1H), 4.97 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 3.62 (s, 3H), 3.35 (s, 3H), 2.97 (dd, J = 8.6, 6.2 Hz, 2H), 2.61 (dd, J = 8.6, 6.3 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C{H} NMR (101 MHz): δ 170.3, 167.2, 154.2, 143.7, 139.4, 126.5, 123.5, 120.5, 118.0, 111.8, 100.7, 60.6, 58.1, 31.2, 30.0, 19.6, 14.5. IR ν: 2852, 1677, 1598, 1354, 1251, 1124, 812 cm^{-1}. HRMS (FD) m/z: [M]$^+$ calcd for $C_{17}H_{21}NO_5^+$, 319.1420; found, 319.1415.

*(E)-Ethyl 3-(5-Hydroxy-1-methyl-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl)acrylate (**5b**).* Substrate **5a** (17.7 mg, 0.1 mmol) was olefinated using ethyl acrylate (16.3 μL, 0.15 mmol, 1.5 equiv) and PhCO$_3^t$Bu (18.6 μL, 0.1 mmol, 1.0 equiv) following the general procedure, and the sample was purified by preparative TLC (PE/EtOAc, 2:1) to give **5b** as a yellow oil (7.4 mg, 27%). (The product is not stable, as after the sample solution in $CDCl_3$ was stored overnight at room temperature and was measured again, many new peaks appeared.) ^{1}H NMR (300 MHz): δ 7.97 (d, J = 16.0 Hz, 1H), 7.40 (d, J = 8.6 Hz, 1H), 6.64 (d, J = 8.6 Hz, 1H), 6.45 (d, J = 15.9 Hz, 1H), 5.88 (s, 1H), 4.27 (q, J = 7.2 Hz, 2H), 3.36 (s, 3H), 2.96−2.83 (m, 2H), 2.67 (dd, J = 8.8, 6.2 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H).

*(E)-Ethyl 3-[5-Ethoxy-1-(methoxymethyl)-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]acrylate (**6b**).* Substrate **6a** (81.6 mg, 0.35 mmol) was olefinated using ethyl acrylate (57.0 μL, 0.525 mmol, 1.5 equiv), PhCO$_3^t$Bu (67.0 μL, 0.35 mmol, 1.0 equiv) following the general procedure, and the sample was purified by flash column chromatography (PE/EtOAc, 3:1) to give a mixture of **6b-a** and **6b-b** as a yellow oil (50.8 mg, 44%, **6b−a**/**6b−b** = 9.1:1) and **6b−c** as a yellow oil (1.7 mg, 1.5%). ^{1}H NMR (400 MHz) (**6b−a**): δ 7.91 (d, J = 16.2 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.11 (d, J = 8.5 Hz, 1H), 6.43 (d, J = 16.1 Hz, 1H), 5.31 (s, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.86 (q, J = 6.4 Hz, 2H), 3.41 (s, 3H), 2.97 (t, J = 7.2 Hz, 2H), 2.76−2.63 (m, 2H), 1.43 (t, J = 6.3 Hz, 3H), 1.34 (t, J = 7.2 Hz, 3H). ^{13}C{H} NMR (101 MHz) (**6b−a**): δ 171.1, 167.3, 155.6, 142.6, 139.2, 126.9, 123.9, 120.3, 118.2, 112.5, 74.0, 70.8, 60.5, 56.5, 31.3, 19.1, 15.6, 14.4. IR (**6b−a**) ν: 2976, 1711, 1680, 1626, 1598, 1393, 1166, 1041 cm^{-1}. HRMS (**6b−a**) (FD) m/z: [M]$^+$ calcd for $C_{18}H_{23}NO_5$, 333.1576; found, 333.1575. ^{1}H NMR (400 MHz) (**6b−c**): δ 7.64 (d, J = 16.0 Hz, 1H), 7.12 (d, J = 1.3 Hz, 1H), 6.79 (d, J = 1.4 Hz, 1H), 6.41 (d, J = 15.9 Hz, 1H), 5.31 (s, 2H), 4.27 (q, J = 7.1 Hz, 2H), 4.08 (q, J = 7.0 Hz, 2H), 3.41 (s, 3H), 2.95−2.92 (m, 2H), 2.66 (dd, J = 8.4, 6.3 Hz, 2H), 1.44 (t, J = 7.0 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C{H} NMR (101 MHz) (**6b-c**): δ 171.4, 167.0, 156.0, 144.7, 141.3, 134.5, 118.5, 117.2, 109.0, 106.1, 74.2, 64.2, 60.7, 56.5, 31.2, 18.5, 15.0, 14.5. IR (**6b−c**) ν: 2979, 2931, 1690, 1601, 1270, 1177 cm^{-1}. HRMS (**6b−c**) (FD) m/z: [M]$^+$ calcd for $C_{18}H_{23}NO_5^+$, 333.1576; found, 333.1575.

*(E)-Ethyl 3-[1-(4-Acetoxybenzyl)-5-ethoxy-2-oxo-1,2,3,4-tetrahydroquinolin-6-yl]acrylate (**7b**).* Substrate **7a** (33.9 mg, 0.1 mmol) was olefinated using ethyl acrylate (16.3 μL, 0.15 mmol, 1.5 equiv) and PhCO$_3^t$Bu (18.6 μL, 0.1 mmol, 1.0 equiv) following the general procedure, and the sample was purified by flash column chromatography (PE/EtOAc, 3:1 to 2:1) to give **7b** as a yellow oil (21.0 mg, 48%, C6/others > 20:1). ^{1}H NMR (400 MHz): δ 7.87 (d, J = 16.1 Hz, 1H), 7.34 (d, J = 8.7 Hz, 1H), 7.23−7.21 (m, 2H), 7.05−7.03 (m, 2H), 6.69 (d, J = 8.7 Hz, 1H), 6.37 (d, J = 16.1 Hz, 1H), 5.15 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 3.87 (q, J = 7.0 Hz, 2H), 3.02 (dd, J = 8.6, 6.1 Hz, 2H), 2.78−2.72 (m, 2H), 2.28 (s, 3H), 1.44 (t, J = 7.0 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H). ^{13}C{H} NMR (101 MHz): δ 170.4, 169.6, 167.3, 155.8, 149.9, 142.8, 139.1, 134.4, 127.7, 126.8, 123.6, 122.0, 120.5, 118.1, 112.0, 70.8, 60.6, 45.9, 31.4, 21.3, 19.2, 15.7, 14.5. IR ν: 2927, 1761, 1681, 1371, 1166 cm^{-1}. HRMS (FD) m/z: [M]$^+$ calcd for $C_{25}H_{27}NO_6^+$, 437.1838; found, 437.1837.

*(E)-5-Hydroxy-6-{2-[5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl]vinyl}-1-methyl-3,4-dihydroquinolin-2(1H)-one (**5c**) and 2-[5-(2-Hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl]-6-methyl-8,9-dihydrofuro[2,3-f]quinolin-7(6H)-one (**5d**).* Substrate **5a** (44.3 mg, 0.25 mmol) was olefinated using ***trans*-29** (63.8 mg, 0.375 mmol, 1.5 equiv) and PhCO$_3^t$Bu (86.0 μL, 0.45 mmol, 1.8 equiv) for 16 h following the general procedure, and the sample was purified by preparative TLC (PE/EtOAc, 3:1) to give **5c** as a yellow oil (41.4 mg, 48%, dr = 1.3:1) and **5d** as a yellow oil (15.4 mg, 18%, dr not determined). Another reaction was also performed using a mixture of ***trans*-29** and ***cis*-29** as the olefin, and the same results were obtained regarding both the yield and diastereoselectivity. ^{1}H NMR (**5c**) (300 MHz) (two diastereoisomers: A/B = 1:1.3): δ 7.17 (d, J = 8.5 Hz, 1H$_B$), 7.15 (d, J = 8.5 Hz, 1H$_A$), 6.83 (d, J = 16.0 Hz, 1H$_A$), 6.71 (d, J = 15.9 Hz, 1H$_B$), 6.55 (d, J = 8.5 Hz, 1H$_B$), 6.54 (d, J = 8.5 Hz, 1H$_A$), 6.12 (d, J = 15.9 Hz, 1H$_A$), 6.10 (d, J = 15.9 Hz, 1H$_B$), 3.96−3.90 (m, 1H$_A$ and 1H$_B$), 3.33 (s, 3H$_B$), 3.33 (s, 3H$_A$), 2.93−2.86 (m, 2H$_A$ and 2H$_B$), 2.63−2.57 (m, 2H$_A$ and 2H$_B$), 2.04−1.81 (m, 4H$_A$ and 4H$_B$), 1.42 (s, 3H$_B$), 1.32 (s, 3H$_A$), 1.18 (s, 3H$_A$), 1.16 (s, 3H$_B$). ^{13}C{H} NMR (**5c**) (75 MHz): δ 170.6 (A and B), 150.3 (A and B), 141.0 (A and B), 137.7 (A or B), 137.1 (A or B), 125.7 (A or B), 125.6 (A or B), 122.0 (A or B), 121.1 (A or B), 120.3 (A or B), 120.0 (A or B), 113.2 (A and B), 107.5 (A and B), 86.1 (A or B), 86.0 (A or B), 83.6 (A or B), 83.1 (A or B), 72.1 (A or B), 72.0 (A or B), 38.7 (A or B), 38.3 (A or B), 31.2 (A and B), 29.9 (A and B), 27.5 (A and B), 27.0 (A or B), 26.9 (A or B), 26.7 (A or B), 26.5 (A or B), 25.3 (A or B), 23.9 (A or B), 18.4 (A and B). IR (**5c**) ν: 3306, 2972, 2929, 1652, 1624, 1472, 1372, 1126, 1041, 729 cm^{-1}. HRMS (**5c**) (FD) m/z: [M]$^+$ calcd for $C_{20}H_{25}NO_4$, 343.1784; found, 343.1771. ^{1}H NMR (**5d**) (400 MHz) (two diastereoisomers: A and B. Ratio was not determined): δ 7.38 (d, J = 8.5 Hz, 1H$_A$ and 1H$_B$), 6.94 (d, J = 8.5 Hz, 1H$_A$ and 1H$_B$), 6.57 (s, 1H$_A$ and 1H$_B$), 4.05−4.01 (m, 1HA and 1HB), 3.44 (s, 3H$_A$ and 3H$_B$), 3.19−3.14 (m, 2H$_A$ and 2H$_B$), 2.77−2.72 (m, 2H$_A$ and 2H$_B$), 2.52−2.43 (m, 1H$_A$ and 1H$_B$), 2.10−1.97 (m, 3H$_A$ and 3H$_B$), 1.70 (s, 3H$_A$), 1.69 (s, 3H$_B$), 1.31 (s, 3H$_A$), 1.30 (s, 3H$_B$), 1.21 (s, 3H$_B$), 1.20 (s, 3H$_A$). ^{13}C{H} NMR (**5d**) (75 MHz): δ 170.2 (A and B), 162.4 (A and B), 152.4 (A or B), 152.2 (A or B), 137.8 (A or B), 137.6 (A or B), 124.0 (A or B), 123.8 (A or B), 119.0 (A or B), 118.9 (A or B), 110.9 (A or B), 110.8 (A or B), 109.7 (A and B), 101.5 (A or B), 101.3 (A or B), 86.7 (A and B), 81.0 (A or B), 80.7 (A or B), 71.5 (A or B), 71.3 (A or B), 38.6 (A or B), 37.5 (A or B), 31.3 (A and B), 30.3 (A and B), 27.9 (A and B), 27.4 (A or B), 27.1 (A or B), 26.7 (A or B), 26.6 (A or B), 24.7 (A or B), 24.4 (A or B), 18.7 (A or B), 18.6 (A or B). IR (**5d**) ν: 3444, 2975, 2928, 1671, 1632, 1470, 1375, 1127, 1026, 819 cm^{-1}. HRMS (**5d**) (FD) m/z: [M]$^+$ calcd for $C_{20}H_{27}NO_4^+$, 345.1940; found, 345.1944.

(3R,4R*)-4,5-Dihydroxy-3-methoxy-4-(4-methoxyphenyl)-6-[(E)-3-oxobut-1-en-1-yl]-1-{[2-(Trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1H)-one [(±)-**17**].* The substrate (±)-**16** (44.5 mg,

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

0.1 mmol) was olefinated using but-3-en-2-one (12.5 μL, 0.15 mmol, 1.5 equiv) and $PhCO_3^tBu$ (38.0 μL, 0.2 mmol, 2.0 equiv) following the general procedure, and the sample was purified by flash column chromatography (*n*-hexane/EtOAc, 3:1) to give (±)-**17** as a mixture of regioisomers [30.3 mg, 59%, yellow oil, (±)-**17-A**/(±)-**17-B** = 6:1], and (±)-**17-di** (2.9 mg, 5%, yellow oil). ^{1}H NMR (300 MHz) [(±)-**17-A**]: δ 9.52 (s, 1H), 7.82 (d, *J* = 16.5 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.15−7.10 (m, 2H), 6.99 (d, *J* = 8.6 Hz, 1H), 6.84−6.78 (m, 2H), 6.72 (d, *J* = 16.5 Hz, 1H), 5.61 (d, *J* = 10.9 Hz, 1H), 5.01 (d, *J* = 11.1 Hz, 1H), 4.62 (s, 1H), 3.84 (s, 1H), 3.75 (s, 3H), 3.58−3.52 (m, 5H), 2.34 (s, 3H), 0.96−0.93 (m, 2H), −0.03 (s, 9H). ^{13}C{H} NMR (75 MHz) [(±)-**17-A**]: δ 199.3, 165.9, 160.6, 156.9, 139.9, 138.1, 129.5, 128.4, 128.1, 127.0, 119.5, 114.5, 112.6, 108.2, 84.4, 78.2, 72.0, 66.4, 58.9, 55.4, 27.0, 18.1, −1.3. IR [(±)-**17-A**] ν: 3259, 2953, 2926, 1692, 1605, 1369, 1252, 1081, 834 cm^{-1}. HRMS [(±)-**17-A**] (FD) *m*/*z*: [M]$^+$ calcd for $C_{27}H_{35}NO_7Si^+$, 513.2183; found, 513.2208. ^{1}H NMR (400 MHz) [(±)-**17-di**]: δ 9.41 (s, 1H), 7.82 (d, *J* = 16.5 Hz, 1H), 7.75 (d, *J* = 16.5 Hz, 1H), 7.58 (d, *J* = 8.7 Hz, 1H), 7.53 (d, *J* = 2.4 Hz, 1H), 7.05 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 1H), 6.74 (d, *J* = 16.5 Hz, 1H), 6.67 (d, *J* = 16.5 Hz, 1H), 5.64 (d, *J* = 10.9 Hz, 1H), 5.01 (d, *J* = 10.8 Hz, 1H), 4.59 (s, 1H), 3.86 (s, 3H), 3.81 (s, 1H), 3.60 (s, 3H), 3.60−3.53 (m, 2H), 2.37 (s, 2H), 2.36 (s, 3H), 0.96−0.92 (m, 2H), −0.03 (s, 9H). ^{13}C{H} NMR (101 MHz) [(±)-**17-di**]: δ 199.2, 199.1, 165.7, 159.1, 156.8, 139.8, 138.2, 137.9, 129.9, 129.8, 128.9, 128.7, 127.2, 127.2, 124.2, 119.8, 112.1, 111.6, 108.4, 84.3, 78.0, 72.1, 66.4, 59.0, 55.8, 27.4, 27.2, 18.1, −1.3. IR [(±)-**17-di**] ν: 3251, 2954, 1692, 1604, 1368, 1253, 1082, 836 cm^{-1}. HRMS [(±)-**17-di**] (FD) *m*/*z*: [M]$^+$ calcd for $C_{31}H_{39}NO_8Si^+$, 581.2445; found, 581.2443.

(E)-4,5-Dihydroxy-3-methoxy-4-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-6-[2-(2,5,5-trimethyltetrahydro-2H-pyran-2-yl)vinyl]-3,4-dihydroquinolin-2(1H)-one (**19**). Substrate (±)-**16** (111.2 mg, 0.25 mmol) was olefinated using olefin **18** (57.8 mg, 0.375 mmol, 1.5 equiv) and $PhCO_3^tBu$ (86.0 μL, 0.45 mmol, 1.8 equiv) following the general procedure, and the sample was purified by preparative TLC (*n*-hexane/acetone, 6:1) to give **19** as a mixture of regioisomers (75.0 mg, 50%, yellow oil, regioselectivity: 8.8:1, dr = 1:1). ^{1}H NMR (400 MHz) (two diastereoisomers: A and B): δ 9.18 (br s, $1H_A$ or $1H_B$), 9.17 (br s, $1H_A$ or $1H_B$), 7.48 (d, *J* = 8.6 Hz, $1H_A$ and $1H_B$), 7.18−7.13 (m, $2H_A$ and $2H_B$), 6.96 (d, *J* = 8.6 Hz, $1H_A$ and $1H_B$), 6.83−6.80 (m, $2H_A$ and $2H_B$), 6.77 (d, *J* = 16.7 Hz, $1H_A$ and $1H_B$), 6.18 (d, *J* = 16.7 Hz, $1H_A$ or $1H_B$), 6.17 (d, *J* = 16.7 Hz, $1H_A$ or $1H_B$), 5.63 (d, *J* = 10.9 Hz, $1H_A$ and $1H_B$), 4.99 (d, *J* = 10.9 Hz, $1H_A$ and $1H_B$), 4.45 (s, $1H_A$ and $1H_B$), 3.81 (s, $1H_A$ or $1H_B$), 3.80 (s, $1H_A$ or $1H_B$), 3.76 (s, $3H_A$ or $3H_B$), 3.75 (s, $3H_A$ or $3H_B$), 3.59−3.53 (m, $2H_A$ and $2H_B$), 3.58 (s, $3H_A$ or $3H_B$), 3.57 (s, $3H_A$ or $3H_B$), 3.41−3.36 (m, $1H_A$ and $1H_B$), 3.25−3.21 (m, $1H_A$ and $1H_B$), 1.86−1.79 ($1H_A$ and $1H_B$), 1.75−1.67 ($1H_A$ and $1H_B$), 1.52−1.44 ($1H_A$ and $1H_B$), 1.36−1.32 ($1H_A$ and $1H_B$), 1.31 (s, $3H_A$ and $3H_B$), 1.01 (s, $3H_A$ or $3H_B$), 1.00 (s, $3H_A$ or $3H_B$), 0.95−0.91 ($2H_A$ and $2H_B$), 0.79 (s, $3H_A$ and $3H_B$), −0.03 (s, $9H_A$ and $9H_B$). ^{13}C{H} NMR (101 MHz): δ 165.9 (A and B), 160.5 (A and B), 154.7 (A and B), 137.1 (A and B), 134.8, 134.7, 128.8 (A and B), 128.2 (A and B), 127.4, 127.3, 123.3 (A and B), 122.4 (A and B), 114.4 (A and B), 112.3 (A and B), 107.7 (A and B), 84.7 (A and B), 78.3 (A and B), 74.5 (A and B), 73.0, 72.9, 72.1 (A and B), 66.2 (A and B), 58.9 (A and B), 55.4 (A and B), 33.7 (A and B), 31.3, 31.1, 29.9 (A and B), 29.4, 29.2, 26.8 (A and B), 24.2, 24.1, 18.2 (A and B), −1.3 (A and B). IR ν: 3314, 2950, 1690, 1611, 1511, 1441, 1390, 1250, 1083, 834 cm^{-1}. HRMS (FD) *m*/*z*: [M]$^+$ calcd for $C_{33}H_{47}NO_7Si^+$, 597.3122; found, 597.3134.

(E)-4,5-Dihydroxy-6-{2-[5-(2-hydroxypropan-2-yl)-2-methyltetrahydrofuran-2-yl]vinyl}-3-methoxy-4-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1H)-one (**21**). Substrate (±)-**16** (44.5 mg, 0.1 mmol) was olefinated using ***trans*-20** (25.5 mg, 0.15 mmol, 1.5 equiv) and $PhCO_3^tBu$ (34.2 μL, 0.18 mmol, 1.8 equiv) following the general procedure, and the sample was purified by flash column chromatography (*n*-hexane/EtOAc, 3:1) to give **21** as a mixture of regioisomers (32.0 mg, 52%, yellow oil, A/B = 7:1, dr: not determined). From the ^{1}H NMR spectra of **21**, we mainly found two groups of peaks. That is because the ^{1}H NMR spectra of (±)-**21-A** and (±)-**21-B** were highly identical, while the ^{1}H NMR spectra of (±)-**21-C** and (±)-**21-D** were also highly identical. Therefore, we were not able to determine the ratios of (±)-**21-A**/(±)-**21**-B and (±)-**21-C**/(±)-**21-D**, but we assumed that they were both 1:1. Also, because of overlapping of these two groups of peaks, we were not able to determine their ratio. A reaction using a mixture of ***trans*-** and ***cis*-20** (1:1) as the olefin was also performed [0.1 mmol scale for (±)-**16**], and the product **21** was isolated as a mixture of regioisomers (A/B = 5.3:1) (30.0 mg, 50%, mixture of four diastereoisomers). ^{1}H NMR (400 MHz): δ 9.19 (br s, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 7.43 (d, *J* = 8.6 Hz, $1H_A$ and $1H_B$), 7.41 (d, *J* = 8.6 Hz, $1H_C$ and $1H_D$), 7.16−7.11 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 6.93 (d, *J* = 8.6 Hz, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 6.82−6.77 (m, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 6.33 (d, *J* = 16.4 Hz, $1H_C$ or $1H_D$), 6.32 (d, *J* = 16.4 Hz, $1H_C$ or $1H_D$), 6.28 (d, *J* = 16.3 Hz, $1H_A$ or $1H_B$), 6.27 (d, *J* = 16.3 Hz, $1H_A$ or $1H_B$), 5.62 (d, *J* = 10.9 Hz, $1H_A$ and $1H_B$), 5.61 (d, *J* = 10.9 Hz, $1H_C$ and $1H_D$), 4.98 (d, *J* = 11.0 Hz, $1H_A$ and $1H_B$), 4.97 (d, *J* = 11.0 Hz, $1H_C$ and $1H_D$), 4.47 (s, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.91−3.82 (m, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.80 (s, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.75 (s, $3H_A$, $3H_B$, $3H_C$ and $3H_D$), 3.59−3.52 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), 3.57 (s, $3H_A$ and $3H_B$), 3.56 ($3H_C$ and $3H_D$), 2.05−1.73 (m, $4H_A$, $4H_B$, $4H_C$ and $4H_D$), 1.41 (s, $3H_C$ and $3H_D$), 1.40 (s, $3H_A$ and $3H_B$), 1.24 (s, $3H_A$ and $3H_B$), 1.23 (s, $3H_C$ and $3H_D$), 1.14 (s, $3H_C$ and $3H_D$), 1.13 (s, $3H_A$ and $3H_B$), 0.95−0.91 (m, $2H_A$, $2H_B$, $2H_C$ and $2H_D$), −0.03 (s, $9H_A$, $9H_B$, $9H_C$ and $9H_D$). ^{13}C{H} NMR (101 MHz): δ 165.9 (A, B, C, and D), 160.4 (A, B, C, and D), 154.9 (A, B, C, and D), 137.2 (C or D), 137.1 (C or D), 137.0 (A and B), 136.0 (C or D), 135.9 (C or D), 135.6 (A or B), 135.5 (A or B), 128.9 (A and B), 128.8 (C and D), 128.2 (A, B, C, and D), 127.8 (A or B), 127.7 (A or B), 127.6 (C and D), 122.3 (A, B, C, and D), 121.3 (C and D), 120.9 (A and B), 114.4 (A, B, C, and D), 112.2 (A, B, C, and D), 107.7 (A, B, C, and D), 85.8 (C and D), 85.7 (A and B), 84.7 (A, B, C, and D), 83.4 (A and B), 83.2 (C and D), 78.3 (A, B, C, and D), 72.1 (A, B, C, and D), 71.3 (A and B), 71.2 (C and D), 66.2 (A, B, C, and D), 58.9 (A, B, C, and D), 55.4 (A, B, C, and D), 38.7 (C or D), 38.6 (C or D), 38.1 (A and B), 27.5 (A, B, C, and D), 26.6 (A, B, C, and D), 24.3 (A, B, C, and D), 18.1 (A, B, C, and D), −1.3 (A, B, C, and D). IR ν: 3295, 2967, 2929, 1688, 1611, 1511, 1441, 1374, 1082, 835 cm^{-1}. HRMS (FD) *m*/*z*: [M]$^+$ calcd for $C_{33}H_{47}NO_8Si^+$, 613.3071; found, 613.3064.

(E)-4,5-Dihydroxy-6-[2-(5-hydroxy-2,6,6-trimethyltetrahydro-2H-pyran-2-yl)vinyl]-3-methoxy-4-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]methyl}-3,4-dihydroquinolin-2(1H)-one (**25**). Substrate (±)-**16** (44.5 mg, 0.1 mmol) was olefinated using olefin ***cis*-24** (36.4 mg, 0.15 mmol, 1.5 equiv) and $PhCO_3^tBu$ (34.2 μL, 0.18 mmol, 1.8 equiv) following the general procedure.

Before performing purification, the crude sample was deprotected by using the following procedure: The sample was dissolved in THF (2 mL) and TBAF solution (1.0 mL, 1.0 M in THF) was added dropwise. After stirring it for 4 h, the reaction was quenched by adding water. The mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried with $MgSO_4$, and evaporated in vacuo. the sample was purified by preparative TLC (*n*-hexane/EtOAc, 4:1) to give **25** as a single regioisomer (26.3 mg, 43%, yellow oil, dr = 2.2:2.2:1:1). ^{1}H NMR (300 MHz) [two groups of diastereoisomers: (A + B)/(C + D), 2.2:1] 9.21−9.19 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 7.45 (d, *J* = 8.6 Hz, $1H_A$), 7.45 (d, *J* = 8.6 Hz, $1H_A$ and $1H_B$), 7.44 (d, *J* = 8.6 Hz, $1H_C$ and $1H_D$), 7.19−7.14 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 6.96 (d, *J* = 8.7 Hz, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 6.89−6.79 (m, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 6.38−6.26 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 5.64 (d, *J* = 10.9 Hz, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 5.01 (d, *J* = 10.9 Hz, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 4.48 (s, $1H_A$ and $1H_B$), 4.47 (s, $1H_C$ and $1H_D$), 3.95−3.88 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 3.78 (s, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 3.62−3.54 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 3.59 (s, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 2.08−1.70 (m, $4H_A$, $4H_B$, $4H_C$, and $4H_D$), 1.44 (s, $3H_C$ and $3H_D$), 1.42 ($3H_A$ and $3H_C$), 1.26 (s, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 1.16 (s, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 0.98−0.92 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), −0.01 (s, $9H_A$, $9H_B$, $9H_C$, and $9H_D$). ^{13}C{H} NMR (75 MHz): δ 167.2 (A, B, C, and D),

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

161.7 (A, B, C, and D), 156.1 (A, B, C, and D), 138.4 (C and D), 136.8 (A and B), 137.3 (C or D), 137.1 (C or D), 136.8 (A and B), 130.1 (A, B, C, and D), 129.4 (A, B, C, and D), 129.1 (A or B), 129.0 (A or B), 128.9 (C or D), 128.8 (C or D), 123.6 (A or B), 123.5 (A or B), 123.51 (C and D), 122.6 (C or D), 122.5 (C or D), 122.2 (A or B), 122.1 (A or B), 115.6 (A, B, C, and D), 113.5 (A, B, C, and D), 109.0 (A, B, C, and D), 87.1 (C and D), 86.9 (A and B), 85.9 (A, B, C, and D), 84.7 (A and B), 84.4 (C and D), 79.5 (A, B, C, and D), 73.4 (A, B, C, and D), 72.6 (A, B, C, and D), 67.5 (A and B), 67.4 (C and D), 60.1 (A, B, C, and D), 56.6 (A, B, C, and D), 40.0 (C or D), 39.9 (C or D), 39.4 (A and B), 29.0 (C or D), 28.9 (C or D), 28.8 (A and B), 28.7 (A, B, C, and D), 28.0 (C and D), 27.8 (A and B), 25.8 (C and D), 25.6 (A and B), 19.4 (A, B, C, and D), 0.0 (A, B, C, and D). IR ν: 3296, 2956, 2927, 1688, 1611, 1511, 1441, 1250, 1082, 834 cm^{-1}. HRMS (FD) m/z: $[M]^+$ calcd for $C_{33}H_{47}NO_8Si^+$, 613.3071; found, 613.3084.

*(E)-6-[2-(1,3-Dimethyl-4-oxocyclohexyl)vinyl]-4,5-dihydroxy-3-methoxy-4-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)ethoxy]-methyl}-3,4-dihydroquinolin-2(1H)-one (**29**).* Substrate (±)-**27** (103.9 mg, 0.25 mmol) was olefinated using olefin **28** (dr = 5:4, 57.1 mg, 0.375 mmol, 1.5 equiv) and $PhCO_3{}^tBu$ (86.0 μL, 0.45 mmol, 1.8 equiv) following the general procedure, and the sample was purified by flash column chromatography (*n*-hexane/EtOAc, 2.5:1) to give **29** as a yellow oil (48.0 mg, 34%, regioselectivity > 20:1, dr = 1:1:1.6:1.6). ^1H NMR (400 MHz) [two groups of diastereoisomers: (A + B)/(C + D), 1:1.6]: δ 9.18 (s, $1H_A$ and $1H_B$), 9.17 (C and D), 7.49 (d, J = 8.7 Hz, $1H_A$ and $1H_B$), 7.42 (d, J = 8.6 Hz, $1H_C$ and $1H_D$), 7.31−7.21 (m, $5H_A$, $5H_B$, $5H_C$ and $5H_D$), 6.98 (d, J = 8.7 Hz, $1H_A$ and $1H_B$), 6.95 (d, J = 8.6 Hz, $1H_C$ and $1H_D$), 6.82 (d, J = 16.6 Hz, $1H_A$ and $1H_B$), 6.65 (d, J = 16.5 Hz, $1H_C$ and $1H_D$), 6.31 (d, J = 16.6 Hz, $1H_A$ and $1H_B$), 6.18 (d, J = 16.4 Hz, $1H_C$ and $1H_D$), 5.65 (d, J = 10.9 Hz, $1H_A$ and $1H_B$), 5.63 (d, J = 10.9 Hz, $1H_C$ and $1H_D$), 5.02 (d, J = 10.8 Hz, $1H_A$ and $1H_B$), 5.00 (d, J = 10.8 Hz, $1H_C$ and $1H_D$), 4.59 (s, $1H_A$ and $1H_B$), 4.58 (s, $1H_C$ and $1H_D$), 3.80 (s, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 3.59−3.53 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 3.58 (s, $3H_A$ and $3H_B$), 3.57 (s, $3H_C$ and $3H_D$), 2.66−2.46 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 2.37−2.09 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 1.91−1.84 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 1.76−1.68 (m, $1H_C$ and $1H_D$), 1.63−1.55 (m, $1H_A$ and $1H_B$), 1.51−1.43 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 1.40 (s, $3H_C$ and $3H_D$), 1.11 (s, $3H_A$ and $3H_B$), 1.02 (d, J = 6.4 Hz, $3H_C$ and $3H_D$), 0.99 (d, J = 6.5 Hz, $3H_A$ and $3H_B$), 0.95−0.91 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), −0.03 (s, $9H_A$, $9H_B$, $9H_C$, and $9H_D$). $^{13}C\{H\}$ NMR (75 MHz): δ 213.9 (A and B), 213.5 (C and D), 165.8 (A, B, C, and D), 154.5 (A, B, C, and D), 139.9 (A, B, C, and D), 137.2 (A or B), 137.1 (C or D), 137.1 (A or B), 137.0 (C or D), 136.2 (A, B, C, and D), 129.5 (A and B), 129.0 (C and D), 129.0 (A, B, C, and D), 127.2 (A, B, C, and D), 126.6 (A, B, C, and D), 122.8 (C and D), 122.6 (A and B), 119.8 (A, B, C, and D), 112.3 (A and B), 112.2 (C and D), 107.8 (A, B, C, and D), 84.6 (A, B, C, and D), 78.5 (A, B, C, and D), 72.1 [(A and B) or (C and D)], 71.5 [(A and B) or (C and D)], 66.3 [(A and B) or (C and D)], 66.0 [(A and B) or (C and D)], 58.9 (A, B, C, and D), 47.7 (A and B), 46.9 (C or D), 46.8 (C or D), 41.4 (A and B), 40.8 (C and D), 38.7 (A, B, C, and D), 38.5 (A and B), 38.2 (C or D), 38.1 (C or D), 38.0 (C and D), 37.5 (A and B), 30.6 (A, B, C, and D), 18.2 (A, B, C, and D), 14.7 (C and D), 14.6 (A and B), −1.3 (A, B, C, and D). IR ν: 3294, 2955, 2926, 1689, 1612, 1439, 1376, 1246,1079, 836 cm^{-1}. HRMS (FD) m/z: $[M]^+$ calcd for $C_{32}H_{43}NO_6Si^+$, 565.2860; found, 565.2885.

*(E)-4,5-Dihydroxy-6-[2-(4-hydroxy-1,3-dimethylcyclohexyl)-vinyl]-3-methoxy-4-(4-methoxyphenyl)-1-{[2-(trimethylsilyl)-ethoxy]methyl}-3,4-dihydroquinolin-2(1H)-one (**32**).* Substrate (±)-**27** (41.6 mg, 0.1 mmol) was olefinated using olefin **31** (dr = 5:4, 23.1 mg, 0.15 mmol, 1.5 equiv) and $PhCO_3tBu$ (34.2 μL, 0.18 mmol, 1.8 equiv) using the following the general procedure, and the sample was purified by flash column chromatography (*n*-hexane/EtOAc, 3:1 to 1:1) to give **32** as a yellow oil (22.0 mg, 39%, regioselectivity: >20:1, dr = 1:1:1:1). ^1H NMR (400 MHz) [two groups of diastereoisomers: (A + B)/(C+ D), 1:1]: δ 9.13 [s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 9.11 [s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.45 [d, J = 8.6 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.43 [d, J = 8.6 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.31−7.21 (m, $5H_A$, $5H_B$, $5H_C$, and $5H_D$), 6.95 [d, J = 8.6 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.93 [d, J = 8.6 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.63 [d, J = 16.7 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.59 [d, J = 16.7 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.17 [d, J = 16.4 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.16 [d, J = 8.6 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 5.63 (d, J = 10.9 Hz, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 5.00 (d, J = 10.9 Hz, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 4.55 (s, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 3.79 (s, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 3.57 (s, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 3.59−3.53 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 3.15−3.06 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 1.88−1.73 (m, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 1.66−1.20 (m, $4H_A$, $4H_B$, $3H_C$, and $3H_D$), 1.14 (s, $3H_C$ and $3H_D$), 1.07 (t, J = 12.9 Hz, $1H_A$ and $1H_B$), 1.06 (s, $3H_A$ and $3H_B$), 1.01−0.98 (m, $3H_A$, $3H_B$, $3H_C$, and $3H_D$). $^{13}C\{H\}$ NMR (101 MHz): δ 165.8 (A, B, C, and D), 154.4 [(A and B) or (C and D)], 154.3 [(A and B) or (C and D)], 142.3 (A, B, C, and D), 138.0 (A, B, C, and D), 137.2 (A, B, C, and D), 129.5 (A, B, C, and D), 129.0 (A, B, C, and D), 127.1 [(A and B) or (C and D)], 127.0 [(A and B) or (C and D)], 126.7 (A, B, C, and D), 123.3 (A, B, C, and D),121.6 (A, B, C, and D), 112.1 (A, B, C, and D), 107.8 [(A and B) or (C and D)], 107.7 [(A and B) or (C and D)], 84.6 (A, B, C, and D), 78.5 (A, B, C, and D), 76.3 (A, B, C, and D), 72.1 (A, B, C, and D), 66.2 (A, B, C, and D), 58.9 (A, B, C, and D), 46.0 [(A and B) or (C and D)], 44.8 [(A and B) or (C and D)], 37.4 (A, B, C, and D), 37.4 (A, B, C, and D), 37.2 (A, B, C, and D), 34.0 (C and D), 32.9 (A and B), 32.1 [(A and B) or (C and D)], 32.0 [(A and B) or (C and D)], 18.8 [(A and B) or (C and D)], 18.7 [(A and B) or (C and D)], 18.2 (A, B, C, and D), −1.3 (A, B, C, and D). IR ν: 3338, 2952, 2926, 2855, 1689, 1612, 1440, 1375, 1247, 1080, 1043, 804 cm^{-1}. HRMS (FD) m/z: $[M]^+$ calcd for $C_{32}H_{45}NO_6Si^+$, 567.3016; found, 567.3011.

Deprotection of SEM to Complete the Total Syntheses of Yaequinolone Natural Products. *General Procedure for the Deprotection of SEM with TBAF.* In a 10 mL round bottom flask containing the substrate (1.0 equiv) was added a solution of TBAF (1.0 M in THF, 10−15 equiv) (in cases where more concentrated TBAF was required, after mixing TBAF solution with the substrate in the flask, the THF was quickly evaporated using a rotary evaporator and the right amount of THF was then added). The reaction was then left to stir under reflux at 80 °C overnight. The reaction was then quenched by adding water. The mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The sample was purified by flash column chromatography.

General Procedure for the Deprotection of SEM with Me_2AlCl. In a flame-dried Schlenk flask were added substrate (1.0 equiv) and anhydrous DCM (0.4−0.5 M) under N_2. A solution of Me_2AlCl (1.0 in hexanes, 6.0 equiv) was then added dropwise at −78 °C and the reaction was stirred for 1 h before it was warmed up to 0 °C. After stirring it for another 1 h, the reaction was quenched by adding water. The mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried with Na_2SO_4, and concentrated in vacuo to give the hydroxymethyl protected intermediate, which was then mixed with MeOH (0.4−0.5 M) and $^iPr_2NEt$ (7.0 equiv) and heated at 55 °C overnight. The reaction was quenched by adding saturated solution of NH_4Cl and extracted with EtOAc three times. The combined extracts were washed with brine, dried with Na_2SO_4, and concentrated in vacuo. The sample was purified by flash column chromatography.

*(±)-Yaequinolone B. SEM Deprotection of (±)-**17** with TBAF.* 20 mg of (±)-**17** [regioisomers (6:1), 0.039 mmol, 1.0 equiv] and 600 μL TBAF (1.0 M in THF, 15 equiv) solution were used. Purification was performed using *n*-hexane/EtOAc (1:1) as an eluent to give **(±)-yaequinolone B** as a single regioisomer (pale yellow solid, 9.0 mg, 60%). ^1H NMR (400 MHz): δ 9.44 (s, 1H), 7.80 (d, J = 16.5 Hz, 1H), 7.70 (br s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.20−7.13 (m, 2H), 6.86−6.78 (m, 2H), 6.70 (d, J = 16.5 Hz, 1H), 6.40 (d, J = 8.3 Hz, 1H), 4.62 (s, 1H), 3.77 (s, 3H), 3.73 (s, 1H), 3.62 (s, 3H), 2.35 (s, 3H). $^{13}C\{H\}$ NMR (101 MHz): δ 199.3, 165.5, 160.6, 157.5, 138.1, 137.2, 129.8, 128.6, 127.9, 126.8, 119.3, 114.5, 111.2, 107.5, 84.0,

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

78.8, 59.1, 55.5, 27.1. IR ν: 3251, 2926, 1691, 1599, 1257, 1079, 805 cm^{-1}. Its data matched with those reported in the literature.[4c]

*(±)-Penigequinolones A and B. Deprotection of **19** with TBAF.* 23 mg of **19** [regioisomers (8.8:1), dr = 1:1, 0.0385 mmol, 1.0 equiv] and 385 μL TBAF (1.0 M in THF, 10 equiv) solution were first mixed in the reaction flask. After quickly removing the THF using a rotary evaporator, 90 μL THF was added. Purification was performed using *n*-hexane/EtOAc (2:1) as an eluent to give the product as a mixture of regioisomers (A/B = 13.5:1, dr = 1:1) (pale yellow solid, 16.9 mg, 94%). ^{1}H NMR (400 MHz) (Two diastereoisomers): δ 9.12 (br s, $1H_A$ and $1H_B$), 7.84 (br s, $1H_A$ and $1H_B$), 7.40 (d, J = 8.3 Hz, $1H_A$ or $1H_B$), 7.39 (d, J = 8.3 Hz, $1H_A$ or $1H_B$), 7.21−7.16 (m, $2H_A$ and $2H_B$), 6.84−6.80 (m, $2H_A$ and $2H_B$), 6.73 (d, J = 16.3 Hz, $1H_A$ and $1H_B$), 6.35 (d, J = 8.3 Hz, $1H_A$ or $1H_B$), 6.34 (d, J = 8.3 Hz, $1H_A$ or $1H_B$), 6.14 (d, J = 16.7 Hz, $1H_A$ or $1H_B$), 6.13 (d, J = 16.7 Hz, $1H_A$ or $1H_B$), 4.56 (br s, $1H_A$ and $1H_B$), 3.76 (s, $3H_A$ and $3H_B$), 3.70 (d, J = 1.5 Hz, $1H_A$ or $1H_B$), 3.69 (d, J = 1.5 Hz, $1H_A$ or $1H_B$), 3.60 (s, $3H_A$ and $3H_B$), 3.38 (d, J = 11.3 Hz, $1H_A$ or $1H_B$), 3.37 (d, J = 11.3 Hz, $1H_A$ or $1H_B$), 3.24−3.20 (m, $1H_A$ and $1H_B$), 1.84−1.76 (m, $1H_A$ and $1H_B$), 1.73−1.66 (m, $1H_A$ and $1H_B$), 1.51−1.46 (m, $1H_A$ and $1H_B$), 1.30 (s, $3H_A$ and $3H_B$), 1.00 (s, $3H_A$ and $3H_B$), 0.79 (s, $3H_A$ and $3H_B$). ^{13}C{H} NMR (101 MHz): δ 165.8 (A and B), 160.4 (A and B), 155.3 (A and B), 134.5, 134.43, 134.37 (A and B), 129.1 (A and B), 127.6, 127.5, 123.3 (A and B), 122.1 (A and B), 114.4 (A and B), 110.9 (A and B), 107.0 (A and B), 84.3 (A and B), 74.5 (A and B), 72.9 (A and B), 59.0 (A and B), 55.4 (A and B), 33.7 (A and B), 31.2, 31.1, 29.9 (A and B), 29.3 (A and B), 26.8, 26.7, 24.2 (A and B). IR ν: 3269, 2927, 1686, 1616, 1508, 1256, 1079, 806 cm^{-1}. HRMS (FD) m/z: $[M]^+$ calcd for $C_{27}H_{33}NO_6^+$, 467.2308; found, 467.2287. The data matched with those reported in the literature.[4c]

*(±)-Yaequinolone C. Deprotection of **21** with TBAF.* 24 mg of **21** [regioisomers (6.8:1), dr not determined, 0.039 mmol, 1.0 equiv] and 400 μL TBAF (1.0 M in THF, 10 equiv) solution were first mixed in the reaction flask. After quickly removing the THF using a rotary evaporator, 100 μL THF was added. Purification was performed using *n*-hexane/EtOAc (1.5:1) as an eluent to give the product **22** as a mixture of regioisomers (10:1, dr = 1:1:0.6:0.6) (pale yellow solid, 15.0 mg, 79%). ^{1}H NMR (400 MHz), two groups of diastereoisomers: (A + B)/(C + D) = 1:0.6. The NMR data of groups A and B matched with those of **yaequinolone C** reported in the literature.[4c] Therefore, either **(±)-22-A** or **(±)-22-B** is **(±)-yaequinolone C**. The olefin moiety of **(±)-yaequinolone C** has a trans-configuration]: δ 9.16 (A and/or B and/or C and/or D), 9.15 (A and/or B and/or C and/or D), 7.84 (A, B, C, and D), 7.37 [d, J = 8.2 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.36 [d, J = 8.2 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.22−7.17 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 6.85−6.83 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 6.79 [d, J = 16.4 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.78 [d, J = 8.2 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.34−6.21 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 4.56 [s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 4.57 [s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 3.91−3.83 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 3.76 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 3.75 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 3.69−3.68 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 3.60 (s, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 2.04−1.75 (m, $4H_A$, $4H_B$, $4H_C$, and $4H_D$), 1.40 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 1.39 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 1.24 (s, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 1.14 (s, $3H_A$, $3H_B$, $3H_C$, and $3H_D$). ^{13}C{H} NMR (101 MHz): δ 165.7 (A, B, C, and D), 160.4 (A, B, C, and D), 155.4 (A, B, C, and D), 135.7 (A or B or C or D), 135.6 (A or B or C or D), 135.3 (A and/or B and/or C and/or D), 134.5 (A or B or C or D), 134.4 (A or B or C or D), 134.3 (A and/or B and/or C and/or D), 129.2 [(A and B) or (C and D)], 129.1 [(A and B) or (C and D)], 128.0 (A, B, C, and D), 127.9 [(A and B) or (C and D)], 127.8 [(A and B) or (C and D)], 122.0 [(A and B) or (C and D)], 121.9 [(A and B) or (C and D)], 121.3 [(A and B) or (C and D)], 121.0 (A or B or C or D), 120.9 (A or B or C or D), 114.4 (A, B, C, and D), 110.9 (A, B, C, and D), 107.0 (A, B, C, and D), 85.8 [(A and B) or (C and D)], 85.7 [(A and B) or (C and D)], 84.3 (A, B, C, and D), 83.4 [(A and B) or (C and D)], 83.2 [(A and B) or (C and D)], 78.9 (A, B, C, and D), 71.4 [(A and B) or (C and D)], 71.3 [(A and B) or (C and D)], 59.0 (A, B, C, and D), 55.4 (A, B, C, and D), 38.7 (A or B or C or D), 38.6 (A or B or C or D), 38.1 [(A and B) or (C and D)], 27.5 (A, B, C, and D), 26.7 (A, B, C, and D), 26.6 (A, B, C, and D), 24.6 (A or B or C or D), 24.5 (A or B or C or D), 24.3 [(A and B) or (C and D)]. IR ν: 3249, 2966, 2927, 1686, 1602, 1419, 1373, 1254, 1030, 804 cm^{-1}. HRMS (FD) m/z: $[M]^+$ calcd for $C_{27}H_{33}NO_7^+$, 483.2257; found, 483.2262.

*(±)-Aspoquinolones C and D. Deprotection of **25** with Me_2AlCl.* 38 mg of **25** (dr = 2.2:2.2:1:1, 0.062 mmol) was used and the product **26** was isolated as a mixture of diastereoisomers (A/B/C/D = 2.2:2.2:1:1) (pale yellow solid, 22.0 mg, 73%) after purification with *n*-hexane/EtOAc (1:1) as an eluent. ^{1}H NMR (400 MHz), two groups of diastereoisomers: (A + B)/(C + D) = 2.2:1. Aspoquinolones C and D were reported as a mixture and we found out that one of the mixtures matched with the NMR data of group A and the other one matched with those of Group B.[4b] Therefore, we concluded that one of the natural products has a cis-configuration for the olefin moiety and the other has a trans-configuration for the olefin moiety. δ 9.13 (br s, $1H_A$ or $1H_B$), 9.13 (br s, $1H_C$ or $1H_D$), 9.12 (br s, $1H_A$ or $1H_B$), 9.11 (br s, $1H_C$ or $1H_D$), 8.12 (br s, $1H_C$ and $1H_D$), 8.08 (br s, $1H_A$ and $1H_B$), 7.35−7.31 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 7.18−7.14 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 6.82−6.73 (m, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 6.34−6.21 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 4.59−4.57 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 3.90−3.83 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 3.75−3.74 (m, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 3.69−3.68 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 3.60−3.59 (m, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 2.03−1.74 (m, $4H_A$, $4H_B$, $4H_C$, and $4H_D$), 1.40−1.38 (m, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 1.25−1.23 (m, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 1.13 (s, $3H_A$, $3H_B$, $3H_C$, and $3H_D$). ^{13}C{H} NMR (75 MHz): δ 165.9 (A, B, C, and D), 160.4 (A, B, C, and D), 155.4 (A, B, C, and D), 135.7 (C or D), 135.6 (C or D), 135.3 (A or B), 135.2 (A or B), 134.4 (C and D), 134.4 (C and D), 129.2 (A and B), 129.1 (C and D), 128.0 (A and B), 127.9 (C or D), 127.8 (C or D), 122.0 (C and D), 121.9 (A and B), 121.4 (C or D), 121.3 (C or D), 121.0 (A or B), 120.9 (A or B), 114.4 (A, B, C, and D), 110.9 (A, B, C, and D), 107.0 (A, B, C, and D), 85.8 (C and D), 85.7 (A and B), 84.3 (A, B, C, and D), 83.4 (A and B), 83.2 (C and D), 78.9 (A and B), 78.8 (C and D), 71.4 (C and D), 71.3 (A and B), 59.0 (A, B, C, and D), 55.4 (A, B, C, and D), 38.7 (C and D), 38.6 (A and B), 27.7 (C and D), 27.5 (A, B, C, and D), 27.4 (A and B), 26.8 (C or D), 26.7 (C or D), 26.7 (A or B), 26.6 (A or B), 24.6 (C or D), 24.5 (C or D), 24.3 (A and B). IR ν: 3261, 2924, 1686, 1600, 1377, 1262, 1077, 1026, 734 cm^{-1}. HRMS (FD) m/z: $[M]^+$ calcd for $C_{27}H_{33}NO_7^+$, 483.2257; found, 483.2272.

*(±)-Aflaquinolones A, C, and D. Deprotection of **29** with Me_2AlCl.* 40 mg of **29** (dr = 1:1:1.6:1.6, 0.071 mmol) was used and the product **30** was isolated as a mixture of diastereoisomers (dr = 1:1:1:1) (pale yellow solid, 30.0 mg, 97%) after purification with *n*-hexane/EtOAc (1.5:1) as an eluent. ^{1}H NMR (400 MHz) [two groups of diastereoisomers: (A + B)/(C + D) = 1:1, The ^{1}H NMR data of (±)-aflaquinolones A, C, and D matched with those reported in the literature.:[5b] δ 9.11 [br s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 9.09 [br s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 8.35 [br s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 8.33 [br s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.39 (d, J = 8.3 Hz, $1H_A$ and $1H_B$), 7.34−7.25 (m, $5H_A$, $5H_B$, $6H_C$, and $6H_D$), 6.78 (d, J = 16.6 Hz, $1H_C$ and $1H_D$), 6.61 (d, J = 16.5 Hz, $1H_A$ and $1H_B$), 6.39 (d, J = 8.1 Hz, $1H_C$ and $1H_D$), 6.36 (d, J = 8.2 Hz, $1H_A$ and $1H_B$), 6.27 (d, J = 16.6 Hz, $1H_A$ and $1H_B$), 6.13 (d, J = 16.4 Hz, $1H_C$ and $1H_D$), 4.69 [s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 4.67 [s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 3.69 (d, J = 1.6 Hz, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 3.61 (s, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 2.65−2.44 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 2.36−2.31 (m, $1H_C$ and $1H_D$), 2.28−2.21 (m, $1H_A$ and $1H_B$), 2.21−2.08 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 1.76−1.68 (m, $1H_A$ and $1H_B$), 1.62−1.54 (m, $1H_C$ and $1H_D$), 1.43−1.39 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$) 1.39 (s, $3H_C$ and $3H_D$), 1.10 (s, $3H_A$ and $3H_B$), 1.02 (d, J = 6.5 Hz, $3H_C$ and $3H_D$), 0.93 (d, J = 6.5 Hz, $3H_A$ or $3H_B$), 0.92 (d, J = 6.5 Hz, $3H_A$ or $3H_B$). ^{1}H NMR (400 MHz, acetone-d_6): δ 9.62 (br s, $1H_A$ or $1H_B$ or $1H_C$ or $1H_D$), 9.61 (br s, $1H_A$ or $1H_B$ or $1H_C$ or $1H_D$), 9.59 [br s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 9.37 [br s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 9.36 [br s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.53 (d, J = 8.3 Hz, $1H_A$ or $1H_B$), 7.52 (d, J = 8.3 Hz, $1H_A$ or $1H_B$), 7.43 (d, J =

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277

8.4 Hz, $1H_C$ and $1H_D$), 7.37−7.32 (m, $5H_A$, $5H_B$, $5H_C$, and $5H_D$), 6.84 (d, J = 16.7 Hz, $1H_A$ and $1H_B$), 6.65 (d, J = 16.5 Hz, $1H_C$ and $1H_D$), 6.60 [d, J = 8.6 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.57 [d, J = 8.6 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.44 (d, J = 16.6 Hz, $1H_A$ and $1H_B$), 6.37 (s, $1H_A$ or $1H_B$ or $1H_C$ or $1H_D$), 6.36 (s, $1H_A$ or $1H_B$ or $1H_C$ or $1H_D$), 6.36 [s, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.23 (d, J = 16.4 Hz, $1H_C$ and $1H_D$), 3.68 (d, J = 1.4 Hz, $1H_A$, $1H_B$, $1H_C$ and $1H_D$), 3.52 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 3.51 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 2.73−2.47 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 2.22−2.09 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 1.91−1.81 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 1.75−1.67 (m, $1H_A$ and $1H_B$), 1.58−1.49 (m, $1H_C$ and $1H_D$), 1.42 (s, $3H_C$ and $3H_D$), 1.11 (s, $3H_A$ and $3H_B$), 0.95 (d, J = 6.5 Hz, $3H_C$ and $3H_D$), 0.93 (d, J = 6.5 Hz, $3H_A$ or $3H_B$), 0.92 (d, J = 6.5 Hz, $3H_A$ or $3H_B$). $^{13}C\{H\}$ NMR (101 MHz): δ 214.0 [(A and B) or (C and D)], 213.6 [(A and B) or (C and D)], 165.9 (A, B, C, and D), 155.0 (A, B, C, and D), 137.4 (A, B, C, and D), 136.0 (A, B, C, and D), 134.5 [(A and B) or (C and D)], 134.4 [(A and B) or (C and D)], 129.4 (A, B, C, and D), 129.1 [(A and B) or (C and D)], 129.0 [(A and B) or (C and D)], 127.4 [(A and B) or (C and D)], 127.3 [(A and B) or (C and D)], 126.4 (A, B, C, and D), 122.6 (A, B, C, and D), 122.5 [(A and B) or (C and D)], 122.4 [(A and B) or (C and D)], 110.9 [(A and B) or (C and D)], 110.8 [(A and B) or (C and D)], 107.2 (A, B, C, and D), 84.2 (A, B, C, and D), 79.0 (A, B, C, and D), 59.1 (A, B, C, and D), 47.7 (A or B), 47.6 (A or B), 46.9 (C or D), 46.8 (C or D), 41.5 (A and B), 40.8 (C and D), 38.7 (A, B, C, and D), 38.5 [(A and B) or (C and D)], 38.2 [(A and B) or (C and D)], 38.0 (C and D), 37.4 (A and B), 30.6 (A, B, C, and D), 14.7 (A or B or C or D), 14.6 (A or B or C or D), 14.3 [(A and B) or (C and D)]. IR ν: 3221, 2923, 1689, 1377, 1260, 1080, 1026, 800 cm^{-1}. HRMS (FD) m/z: $[M]^+$ calcd for $C_{26}H_{29}NO_5^+$, 435.2046; found, 435.2047.

(±)-Scopuquinolone B. Deprotection of ***32*** *with* Me_2AlCl. 19 mg of **32** (dr = 1:1:1:1, 0.0335 mmol) was used and the product **33** was isolated as a mixture of daistereosiomers (dr = 1:1:1:1) (pale yellow solid, 13.0 mg, 89%) after purification with *n*-hexane/EtOAc (1:1) as an eluent. ^1H NMR (400 MHz, acetone-d_6) [two groups of diastereoisomers: (A + B)/(C + D) = 1:1. The NMR data of groups C and D matched with those of scopuquinolone B reported in the literature.:[6c] δ 9.55 (br s, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 9.33 (br s, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 7.44 [d, J = 8.3 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.42 [d, J = 8.3 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 7.37−7.32 (m, $5H_A$, $5H_B$, $5H_C$, and $5H_D$), 6.65−6.55 (m, $2H_A$, $2H_B$, $2H_C$, and $2H_D$), 6.20 [d, J = 16.5 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 6.17 [d, J = 16.5 Hz, ($1H_A$ and $1H_B$) or ($1H_C$ and $1H_D$)], 3.66 (d, J = 1.5 Hz, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 3.52 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 3.51 [s, ($3H_A$ and $3H_B$) or ($3H_C$ and $3H_D$)], 3.06−2.97 (m, $1H_A$, $1H_B$, $1H_C$, and $1H_D$), 1.81−1.68 (m, $3H_A$, $3H_B$, $3H_C$, and $3H_D$), 1.64−1.27 (m, $3H_A$, $3H_B$, $4H_C$, and $4H_D$), 1.13 (s, $3H_A$ and $3H_B$), 1.07 (t, J = 12.9 Hz, $1H_c$ and $1H_d$), 1.01 (s, $3H_C$ and $3H_D$), 0.98 (d, J = 6.4 Hz, $3H_A$ and $3H_B$), 0.96 (d, J = 6.4 Hz, $3H_A$ and $3H_B$). $^{13}C\{H\}$ NMR (101 MHz, acetone-d_6): δ 166.3 (A, B, C, and D), 156.1 (C and D), 155.9 (A and B), 141.8 (A and B), 140.3 (C and D), 137.6 (A, B, C, and D), 136.9 (A, B, C, and D), 129.7 (A, B, C, and D), 129.6 (A, B, C, and D), 127.5 [(A and B) or (C and D)], 127.5 [(A and B) or (C and D)], 127.4 [(A and B) or (C and D)], 127.3 [(A and B) or (C and D)], 122.6 (A, B, C, and D), 122.3 (A, B, C, and D), 112.1 (A, B, C, and D), 107.7 (A, B, C, and D), 85.8 (A, B, C, and D), 80.0 (A, B, C, and D), 76.8 (A, B, C, and D), 59.0 (A, B, C, and D), 46.9 (C and D), 45.9 (A and B), 37.7 (A, B, C, and D), 37.7 (A, B, C, and D), 37.0 [(A and B) or (C and D)], 36.9 [(A and B) or (C and D)], 34.0 (A and B), 33.1 (C and D), 31.9 [(A and B) or (C and D)], 31.8 [(A and B) or (C and D)], 19.5 [(A and B) or (C and D)], 19.4 [(A and B) or (C and D)]. IR ν: 3274, 2926, 1687, 1620, 1452, 1378, 1261, 1082, 1039, 803 cm^{-1}. HRMS (FD) m/z: $[M]^+$ calcd for $C_{26}H_{31}NO_5^+$, 437.2202; found, 437.2198.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00042.

General schemes for the synthesis of **18**, *trans*-**20**, **28**, **31**, and (±)-**27**; comparison of the ^1H NMR spectra of olefinated product **21** when using *trans*-**20** or a mixture of *trans*- and *cis*-**20**; comparison of the NMR data of natural and synthetic products; and copies of the ^1H and ^{13}C NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

M. Angeles Fernández-Ibáñez − *Van't Hoff Institute for Molecular Sciences, University of Amsterdam, 1098 XH Amsterdam, The Netherlands;* orcid.org/0000-0002-7694-5911; Email: m.a.fernandezibanez@uva.nl

Authors

Wen-Liang Jia − *Van't Hoff Institute for Molecular Sciences, University of Amsterdam, 1098 XH Amsterdam, The Netherlands*

Sabela Vega Ces − *Van't Hoff Institute for Molecular Sciences, University of Amsterdam, 1098 XH Amsterdam, The Netherlands*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.1c00042

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge financial support from NWO through a VIDI grant (723.013.006). W.L.J. gratefully acknowledges financial support from the China Scholarship Council (CSC) (File no. 201606180020).

■ REFERENCES

(1) Simonetti, S. O.; Larghi, E. L.; Kaufman, T. S. The 3,4-dioxygenated 5-hydroxy-4-aryl-quinolin2(1*H*)-one alkaloids. Results of 20 years of research, uncovering a new family of natural products. *Nat. Prod. Rep.* **2016**, *33*, 1425−1446.

(2) Nakaya, T. Anti-brine shrimp substances produced by penicillium sp. NTC-47. *Seikatsu Eisei* **1995**, *39*, 141−143.

(3) (a) Kimura, Y.; Kusano, M.; Koshino, H.; Uzawa, J.; Fujioka, S.; Tani, K. Penigequinolones A and B, pollen-growth inhibitors produced by Penicilium sp., No. 410. *Tetrahedron Lett.* **1996**, *37*, 4961−4964. (b) Hayashi, H.; Nakatani, T.; Inoue, Y.; Nakayama, M.; Nozaki, H. New Dihydroquinolinone Toxic toArtemia salinaProduced byPenicilliumsp. NTC-47. *Biosci., Biotechnol., Biochem.* **1997**, *61*, 914−916. (c) Kusano, M.; Koshino, H.; Uzawa, J.; Fujioka, S.; Kawano, T.; Kimura, Y. Nematicidal Alkaloids and Related Compounds Produced by the Fungus Penicillium cf. simplicissimum. *Biosci., Biotechnol., Biochem.* **2000**, *64*, 2559−2568. (d) He, J.; Lion, U.; Sattler, I.; Gollmick, F. A.; Grabley, S.; Cai, J.; Meiners, M.; Schünke, H.; Schaumann, K.; Dechert, U.; Krohn, M. Diastereomeric Quinolinone Alkaloids from the Marine-Derived FungusPenicillium-janczewskii. *J. Nat. Prod.* **2005**, *68*, 1397−1399.

(4) (a) Uchida, R.; Imasato, R.; Shiomi, K.; Tomoda, H.; Ōmura, S. Yaequinolones J1 and J2, Novel Insecticidal Antibiotics fromPenicilliumsp. FKI-2140. *Org. Lett.* **2005**, *7*, 5701−5704. (b) Scherlach, K.; Hertweck, C. Discovery of aspoquinolones A-D, prenylated quinoline-2-one alkaloids from Aspergillus nidulans, motivated by genome mining. *Org. Biomol. Chem.* **2006**, *4*, 3517−3520. (c) Uchida,

R.; Imasato, R.; Yamaguchi, Y.; Masuma, R.; Shiomi, K.; Tomoda, H.; Ōmura, S. Yaequinolones, new insecticidal antibiotics produced by *penicillium* sp. FKI-2140. I. Taxonomy, fermentation, isolation and biological activity. *J. Antibiot.* **2006**, *59*, 646−651.
(5) (a) Uchida, R.; Imasato, R.; Tomoda, H.; Ōmura, S. Yaequinolones, new insecticidal antibiotics produced by *penicillium* sp. FKI-2140. II. Structural elucidation. *J. Antibiot.* **2006**, *59*, 652−658. (b) Neff, S. A.; Lee, S. U.; Asami, Y.; Ahn, J. S.; Oh, H.; Baltrusaitis, J.; Gloer, J. B.; Wicklow, D. T. Aflaquinolones A-G: Secondary Metabolites from Marine and Fungicolous Isolates of Aspergillus spp. *J. Nat. Prod.* **2012**, *75*, 464−472. (c) An, C.-Y.; Li, X.-M.; Luo, H.; Li, C.-S.; Wang, M.-H.; Xu, G.-M.; Wang, B.-G. 4-Phenyl-3,4-dihydroquinolone Derivatives from Aspergillus nidulans MA-143, an Endophytic Fungus Isolated from the Mangrove Plant Rhizophora stylosa. *J. Nat. Prod.* **2013**, *76*, 1896−1901. (d) Chen, M.; Shao, C.-L.; Meng, H.; She, Z.-G.; Wang, C.-Y. Anti-Respiratory Syncytial Virus Prenylated Dihydroquinolone Derivatives from the Gorgonian-Derived Fungus Aspergillus sp. XS-20090B15. *J. Nat. Prod.* **2014**, *77*, 2720−2724.
(6) (a) Shao, C.-L.; Xu, R.-F.; Wang, C.-Y.; Qian, P.-Y.; Wang, K.-L.; Wei, M.-Y. Potent antifouling marine dihydroquinolin-2(1*H*)-one-containing alkaloids from the gorgonian coral-derived fungus *scopulariopsis* sp. *Mar. Biotechnol.* **2015**, *17*, 408−415. (b) Shao, C.-L.; Chao, R.; Xu, R.-F.; Cao, F.; Wei, M.-Y. Scopuquinolone A, a new terpenoid dihydroquinolone alkaloid from a gorgonian coral-derived *scopulariopsis* sp. Fungus. *Chin. J. Mar. Drugs* **2016**, *35*, 1−5. (c) Mou, X.-F.; Liu, X.; Xu, R.-F.; Wei, M.-Y.; Fang, Y.-W.; Shao, C.-L. Scopuquinolone B, a new monoterpenoid dihydroquinolin-2(1H)-one isolated from the coral-derived Scopulariopsis sp. fungus. *Nat. Prod. Res.* **2018**, *32*, 773−776.
(7) Only two members of this family of natural products have a trans-configuration for the two oxygenated functional groups, see: refs 3d and 5b.
(8) Li, X.; Huo, X.; Li, J.; She, X.; Pan, X. A Concise Synthesis of (±)-Yaequinolone A2. *Chin. J. Chem.* **2009**, *27*, 1379−1381.
(9) Vece, V.; Jakkepally, S.; Hanessian, S. Total synthesis and absolute stereochemical assignment of the insecticidal metabolites yaequinolones J1 and J2. *Org. Lett.* **2018**, *20*, 4277−4280.
(10) (a) Schwan, J.; Kleoff, M.; Hartmayer, B.; Heretsch, P.; Christmann, M. Synthesis of quinolinone alkaloids *via* aryne insertions into unsymmetric imides in flow. *Org. Lett.* **2018**, *20*, 7661−7664. (b) Schwan, J.; Kleoff, M.; Heretsch, P.; Christmann, M. Five-step synthesis of yaequinolones J1 and J2. *Org. Lett.* **2020**, *22*, 675−678.
(11) Li, L.; Chen, Z.; Zhang, X.; Jia, Y. Divergent strategy in natural product total synthesis. *Chem. Rev.* **2018**, *118*, 3752−3832.
(12) (a) Lam, N. Y. S.; Wu, K.; Yu, J.-Q. Advancing the logic of chemical synthesis: C-H activation as strategic and tactical disconnections for C-C bond construction. *Angew. Chem., Int. Ed.* **2021**, *60*, 2−26. (b) Hong, B.; Luo, T.; Lei, X. Late-Stage Diversification of Natural Products. *ACS Cent. Sci.* **2020**, *6*, 622−635.
(13) (a) Jia, W.-L.; Westerveld, N.; Wong, K. M.; Morsch, T.; Hakkennes, M.; Naksomboon, K.; Fernández-Ibáñez, M. Á. Selective C-H Olefination of Indolines (C5) and Tetrahydroquinolines (C6) by Pd/S,O-Ligand Catalysis. *Org. Lett.* **2019**, *21*, 9339−9342. For other examples of S,O-bidentate ligand, see: (b) Naksomboon, K.; Valderas, C.; Gómez-Martínez, M.; Álvarez-Casao, Y.; Fernández-Ibáñez, M. Á. S,O-Ligand-Promoted Palladium-Catalyzed C-H Functionalization Reactions of Nondirected Arenes. *ACS Catal.* **2017**, *7*, 6342−6346. (c) Naksomboon, K.; Álvarez-Casao, Y.; Uiterweerd, M.; Westerveld, N.; Maciá, B.; Fernández-Ibáñez, M. Á. S,O-ligand-promoted palladium-catalyzed C-H olefination of arenes with allylic substrates. *Tetrahedron Lett.* **2018**, *59*, 379−382. (d) Álvarez-Casao, Y.; Fernández-Ibáñez, M. Á. S,O-Ligand-Promoted Pd-Catalyzed C-H Olefination of Thiophenes. *Eur. J. Org. Chem.* **2019**, 1842−1845. (e) Naksomboon, K.; Poater, J.; Bickelhaupt, F. M.; Fernández-Ibáñez, M. Á. para-Selective C-H Olefination of Aniline Derivatives via Pd/S,O-Ligand Catalysis. *J. Am. Chem. Soc.* **2019**, *141*, 6719−6725. Jia, W.-L. Palladium catalyzed C−H functionalization of amine derivatives and its application in total synthesis. PhD Thesis, University of Amsterdam, 2021. https://hdl.handle.net/11245.1/2726566f-bb12-4ba8-a0ba-104f0985f844.
(14) (a) Ryabov, A. D.; Sakodinskaya, I. K.; Yatsimirsky, A. K. Kinetics and mechanism of ortho-palladation of ring-substituted NN-dimethylbenzylamines. *J. Chem. Soc., Dalton Trans.* **1985**, 2629−2638. (b) Labinger, J. A.; Bercaw, J. E. Understanding and exploiting C-H bond activation. *Nature* **2002**, *417*, 507−514.
(15) Cyclized product of **5b** was observed after leaving the $CDCl_3$ solution of **5b** overnight at room temperature.
(16) We used MOM as the protecting group for the nitrogen atom. However, although the C−H olefination of the MOM-protected substrate works, we were not able to remove the MOM protecting group after the C−H functionalization step.
(17) We speculated that the racemization can take place at the allylic position via anti-Tsuji−Trost and Tsuji−Trost processes.
(18) We tried to deprotect the TMS and SEM at the same time using concentrated TBAF (4.0 M). However, no desired product was detected after refluxing overnight.
(19) Jaegli, S.; Vors, J.-P.; Neuville, L.; Zhu, J. Palladium-catalyzed domino Heck/cyanation: synthesis of 3-cyanomethyloxindoles and their conversion to spirooxoindoles. *Tetrahedron* **2010**, *66*, 8911−8921.
(20) It was not possible to separate the diastereoisomers by flash column chromatography.
(21) Castelli, R.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. 2,2-Dimethyl-4-(4-methoxy-phenoxy) butanoate and 2,2-dimethyl-4-azido butanoate: two new pivaloate-ester-like protecting groups. *Org. Lett.* **2013**, *15*, 2270−2273.
(22) Oniciu, D. C.; Bell, R. P. L.; McCosar, B. H.; Bisgaier, C. L.; Dasseux, J. L. H.; Verdijk, D.; Relou, M.; Smith, D.; Regeling, H.; Leemhuis, F. M. C.; Ebbers, E. J.; Mueller, R.; Zhang, L.; Pop, E.; Cramer, C. T.; Goetz, B.; McKee, A.; Pape, M. E.; Krause, B. R. Syntheses of pantolactone and pantothenic acid derivatives as potential lipid regulating agents. *Synth. Commun.* **2006**, *36*, 365−391.
(23) Daub, M. E.; Prudhomme, J.; Mamoun, C. B.; Roch, K. G. L.; Vanderwal, C. D. Antimalarial properties of simplified kalihinol analogues. *ACS Med. Chem. Lett.* **2017**, *8*, 355−360.
(24) Vidari, G.; Di Rosa, A.; Zanoni, G.; Bicchi, C. Enantioselective synthesis of each stereoisomer of the pyranoid linalool oxides: the linalool route. *Tetrahedron* **1999**, *10*, 3547−3557.
(25) Zheng, S.; Laxmi, Y. R. S.; David, E.; Dinkova-Kostova, A. T.; Shiavoni, K. H.; Ren, Y.; Zheng, Y.; Trevino, I.; Bumeister, R.; Ojima, I.; Wigley, W. C.; Bliska, J. B.; Mierke, D. F.; Honda, T. Synthesis, chemical reactivity as Michael acceptors, and biological potency of monocyclic cyanoenones, novel and highly potent anti-inflammatory and cytoprotective agents. *J. Med. Chem.* **2012**, *55*, 4837−4846.
(26) Honda, T.; David, E.; Mierke, D. Monocyclic cyanoenones and methods of use thereof. WO 2010011782 A1, Jan 28, 2010.
(27) Liu, B.; Fan, Y.; Gao, Y.; Sun, C.; Xu, C.; Zhu, J. Rhodium(III)-Catalyzed N-Nitroso-Directed C-H Olefination of Arenes. High-Yield, Versatile Coupling under Mild Conditions. *J. Am. Chem. Soc.* **2013**, *135*, 468−473.
(28) Beshore, D. C.; Mohanty, S. K.; Latthe, P. R.; Kuduk, S. D.; Hoyt, S. B. Quinazoline compounds useful as m1 receptor positive allosteric modulators. WO 2017155816 A1, Sept 14, 2017.
(29) Chen, W.; Sun, C.; Zhang, Y.; Hu, T.; Zhu, F.; Jiang, X.; Abame, M. A.; Yang, F.; Suo, J.; Shi, J.; Shen, J.; Aisa, H. A. Oxidative aromatization of 3,4-dihydroquinolin-2(1*H*)-ones to quinolin-2(1*H*)-ones using transition-metal-activated persulfate salts. *J. Org. Chem.* **2019**, *84*, 8702−8709.

https://doi.org/10.1021/acs.joc.1c00042
J. Org. Chem. 2021, 86, 6259−6277