Title

Synthesis of Naturally Racemic Marilines B & C through Multicomponent Reactions Involving ortho -Quinone Methides and Various Nitrogen Nucleophiles

Authors

Wong, Yuk Fai
Pettus, Thomas RR

Publication Date

2023

DOI

10.1055/s-0041-1738443

Synthesis of Naturally Racemic Marilines B-C through Multi-Component Reactions Involving o-QMs and Various Nitrogen Nucleophiles

Journal:	*SYNTHESIS*
Manuscript ID	SS-2023-04-0163-OP.R1
Manuscript Type:	Original Paper
Date Submitted by the Author:	02-May-2023
Complete List of Authors:	Wong, Yuk Fai; University of California Santa Barbara, Chemistry Pettus, Tom; University of California Santa Barbara, Chemistry
Keywords:	natural products, marilines, imines, dihydrooxazoles, anilines, phthalimidines, salicylaldehydes, isoindolin-1-ones
Abstract:	The first total synthesis of (±)-marlines B & C is reported as well as a failed approach to (±) marline A using our recently developed multicomponent reaction method, that involves interception of o-quinone methides (o-QMs) with various nitrogen nucleophiles to provide easy assembly of various benzylic amine cores with diverse substituents

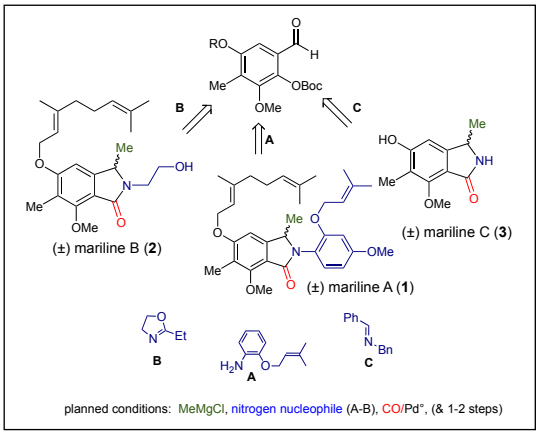
Synthesis Paper / PSP / Special Topic

Synthesis of Naturally Racemic Marilines B-C through Multi-Component Reactions Involving *o*-QMs and Various Nitrogen Nucleophiles

Yuk Fai Wong[a]
Thomas R. R. Pettus*[a]

[a]Department of Chemistry and Biochemistry, University of California at Santa Barbara, Santa Barbara, California, 93106, USA .

trrpettus@ucsb.edu



Received:
Accepted:
Published online:
DOI:

Abstract Herein, **we report the first total synthesis of** (±)-marlines B & C as well as a failed approach to (±) marline A using our recently developed multicomponent reaction method, which involve interception of *o*-quinone methide (*o*-QMs) with various nitrogen nucleophiles to provide easy assembly of various benzylic amine cores with diverse substituents.

Key words *o*-quinone methides, marilines, imine, dihydrooxazole, aniline, isoindolin-1-one, phthalimidine, salicylaldehyde

Numerous phthalimidines found in nature display a wide range of biological activities. These compounds are typically secondary metabolites isolated from bacteria, plants, and fungi. Among phthalimidines, the marilines A-C (**1-3**) require several unique post-biosynthetic reactions. Bringmann and König first reported their isolation in 2012 from the fungus *Stachylidium*, affiliated with the sea sponge *Callyspongia cf. C. flammea*. They separated the enantiomers of (±)-marline A (**1**) and determined that both inhibited leukocyte elastase (HLE) with the same IC_{50} of 0.86 μM, whereas mariline B and C (**2-3**) showed similar antagonistic activity toward the cannabinoid receptor CB2 (5.9 μM for both).[1] Although the authors determined that the constituents of the mariline natural product family were *racemic*, they speculated that *racemization* may have occurred after the biosynthesis during isolation under either acidic or basic conditions. However, after enantiomeric HPLC separation of the mariline A (**1**) *racemate*, remarkably the optical activity of each respective enantiomers A_1 and A_2 was found to remain unchanged upon submission to increasing concentrations of either HCl or KOH.

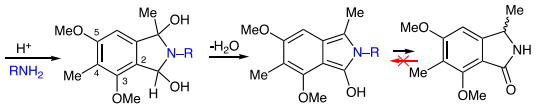


Figure 1: Analog syntheses by Schmaltz, ultimately created into an enantioselective method by Seidel,[3] if R = -Aryl-*ortho*-O-*t*-Bu

In 2015 Schmalz reported syntheses of several analogs of the mariline A-C (**1-3**) as well as several related *iso*-indolinones (*Figure 1*).[2] Their strategy involved a condensation of 2-formal-3,5-dimethoxy-4-methyl-acetophenone with either an aryl or alkyl amine as the supposed non-enzymatic step in the respective biosynthesis via an evidently *irreversible* tautomerization of their respective isoindole intermediates.

Seidel and coworkers, who were likely motivated by the observation that the respective enantiomers of mariline A (**1**) (A1 and A2) displayed different levels of anti-cancer activity toward other cell lines as well as *plasmodium* parasites.[1] They subsequently developed a method facilitating the *first* enantioselective synthesis of a member of this natural product family.[3] They finished a synthesis of (–)-mariline A (**1**) in ten pots from 3,5-dihydroxy-4-methylbenzoic acid and 93% *ee* by deploying an organocatalytic phosphoric acid in the eighth pot for protonation of the isoindole intermediate. Thus, they demonstrated that Schmaltz's post-biosynthetic condensation could indeed proceed in enantioselective fashion in the laboratory. However, this breakthrough enantioselective method was only applied to condensations with *N*-arylated amines that displayed an *ortho*-*t*-butyl ether. Nevertheless, because of the biological activity of the marilines and related phthalimidines, research aimed at improving natural cultivation and refining synthetic strategies has continued.[4]

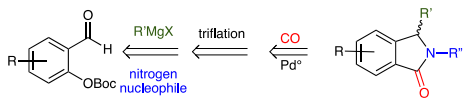
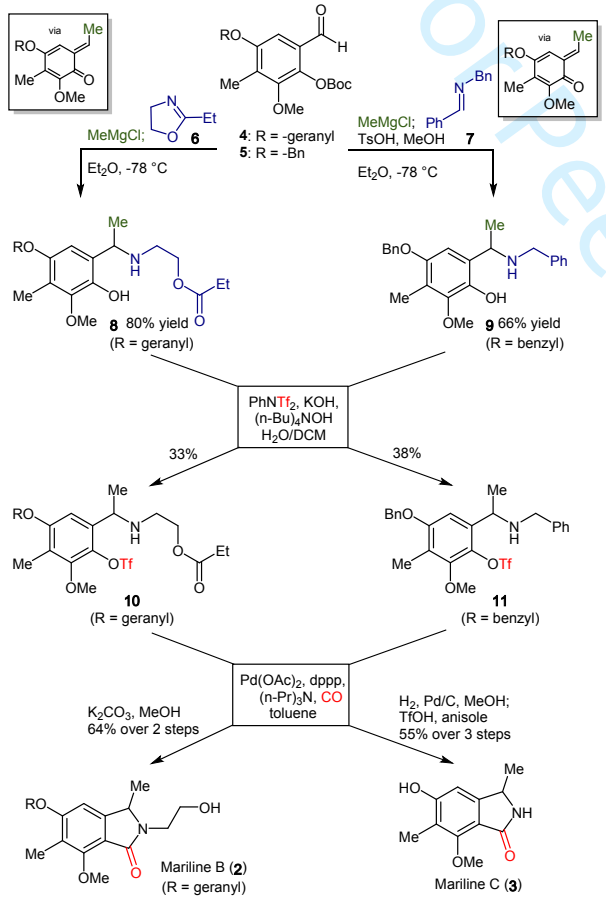


Figure 2: Our strategy for exploration of mariline chemical space

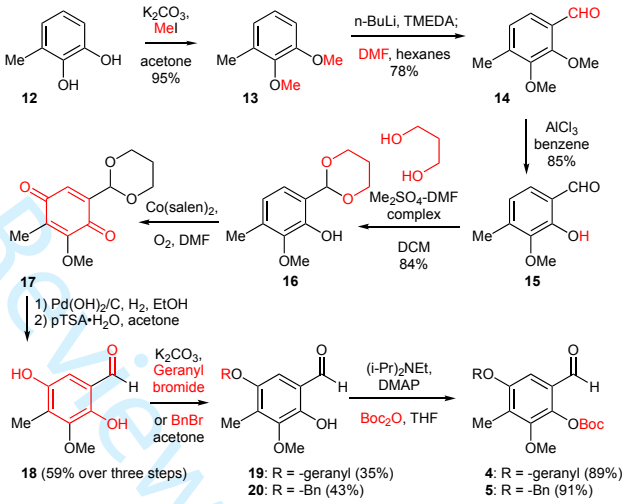
Our interests in constructing (±)-marilines A-C (**1-3**) aimed to deploy a novel synthetic strategy that might prove amenable to facile construction of many analogs, thereby simplifying the exploration of structural space surrounding the family (*Figure 2*). We imagined deploying various nucleophilic nitrogen species in our multicomponent reaction (MCR) involving o-quinone methides (o-QM) generated from assorted *o*-OBoc salicylic aldehydes and Grignard reagents (Figure 2).[5,6,14] In this manner, we imagined rapidly constructing a wide range of phthalimides from combining variations among three components, whereupon triflation and carbonylation would yield varied phthalimidines.[7]

Scheme 1: Syntheses of marlines B-C (**2-3**) using MCR.



To test this notion, we first prepared the respective geranylated and benzylated salicylaldehydes **4** & **5**, as shown in *scheme 2*. These compounds were then submitted separately to our recently reported conditions for nitrogen incorporation *(Scheme 1)*.[6a,b] Following our standard *o*-QM generation protocol,[5b] we found that addition of methyl magnesium chloride to either substrate initiated the desired reaction cascade. In this process, 1,2-addition of the Grignard reagent to the respective aldehyde results in an alkoxide that undergoes subsequent BOC migration and β-elimination to afford the corresponding (*o*-QM) intermediate, which prove extremely reactive. However, in our the new methods,[6a,b] these intermediates can be intercepted with different nitrogen nucleophiles. For example, after low temperature generation of the corresponding *o*-QM followed by addition of the dihydrooxazole **6** and slowly warming to room temperature, the method produced the benzylic amine **8** in an 80% yield. On the other hand, introduction of the imine **7**[13] followed by an acidic aqueous work-up yielded the desired *bis*-benzylic amine **9** in 66% yield.[6b] With these two phenolic materials (**8-9**) in hand, we next required conditions for selective phenol triflation in the presence of a *free* amine. To accomplish this task, we deployed biphasic conditions first reported by Sonesson[8] and isolated moderate yields of the respective triflates **10-11** (33% & 38%, respectively). Using slightly modified palladium carbonylation conditions to those first reported by Crisp,[9] we observed the corresponding phthalimidines to smoothly form. However, synthesis of (±)-mariline B (**2**) required an *in-situ* saponification of its ethyl ester intermediate (64% over two steps), whereas, completion of (±)-mariline C (**3**) required hydrogenolysis of the phenolic benzyl group followed by triflic acid deprotection of its benzyl-amine (55% over three steps).

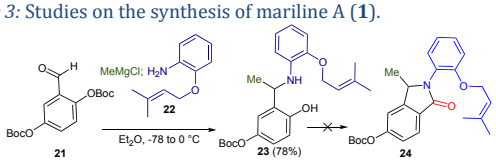
Scheme 2: Syntheses of salicylaldehyde precursors **4** & **5**



The MCR precursors, the O-geranylated aldehyde **4** and the O-benzylated aldehyde **5**, were constructed by us in short order from commercial 3-methylbenzene-1,2-diol **12**. Standard phenolic *per*-methylation afforded the *bis*-methyl ether **13** in a nearly quantitative yield (95%). Directed lithiation and formylation proceeded smoothly to afford the benzaldehyde **14** (78%). Further treatment with aluminum trichloride selectively deprotected the methyl ether closest to the aldehyde producing the salicylaldehyde **15** (85%). However, we found oxidation to the quinone required that the electron deficient carbonyl be protected as its corresponding acetal **16** (84%). *p*-Oxidation of the phenol using $Co(salen)_2$ catalyst[10] then proceeded well and afforded the *p*-quinone **17**. This material was immediately reduced with Pearlman's catalyst and hydrogen to afford the corresponding hydroquinone, whereupon treatment with tosylic acid in acetone afforded the salicylaldehyde **18** (59%, over three steps). At this juncture, we require two different R-residues on the phenol distal to the aldehyde to reach the geranylated marilines A & B (**1-2**) and the unprenylated mariline C (**3**). Respective etherification with geranyl bromide and benzyl bromide in acetone afforded similarly moderate

yields of the corresponding ethers **19** (35% geranyl) & **20** (43% benzyl). Separate protection with Boc_2O using our standard conditions produced the desired benzaldehydes **4** & **5** (89%, 91% respectively) for the MCRs described in *Scheme 1*.

Scheme 3: Studies on the synthesis of mariline A (**1**).



We speculated that completion of mariline A (**1**) might be accomplished using a similar strategy to that employed for mariline C (**3**) (*scheme 3*). However, for this endeavor we would directly use the aniline **22**[11] to conclude our MCR procedure, because necessity had required it; as condensation of aniline **22** with either propionaldehyde or isobutyraldehyde failed to afford a sufficiently pure imine to proceed. For our model study, we decided to test the combination of the previously prepared *o*-OBoc salicylic aldehyde **21**[12] with methyl Grignard, followed by addition of the known aniline **22**. We were elated to find that this reaction smoothly produced the benzylic amine **23** (78%) yield, because the corresponding *o*-QM reactions with aliphatic amines had previously failed in our hands to afford the corresponding products. However, unfortunately application of the same modified Crisp triflation and carbonylation procedure, previously used, failed to yield the heterocyclic ring in phthalimidine **24** in this case—this shortcoming was presumably due to the reduced nucleophilicity of the aryl amine, as compared to the prior successful aliphatic amine examples.

In conclusion, by demonstrating the generality of our MCR method with several nitrogen nucleophiles we have completed the first total syntheses of (±)-marlines B-C (**2-3**), yet failed to reach mariline A (1). This letter provides evidence that our MCR methods can address structural diversity amongst benzylic amines and phthalimidines. Specifically, we have shown that various *o*-QM intermediates can be engaged by anilines, dihydrooxazoles, and imines to arrive at *N*-arylated, *N*-hydroxyl ethylated, and *N*-free amines respectively. The N-aliphatic substrates undergo triflation and directed carbonylation to provide phthalimidines with assorted purported biological activities.

The experimental section has no title; please leave this line here.

In reactions where water was not present as a solvent, reagent, or byproduct, the glassware was flame dried, and the reactions were carried out under an inert atmosphere of nitrogen. Reactions were monitored by analytical thin-layer chromatography on EMD silica gel 60 F254 plates; visualization was affected by ultraviolet light (254 nm), *p*-anisaldehyde or potassium permanganate stains. Diethyl ether and toluene were distilled from sodium and benzophenone. NMR spectra were recorded at 400, 500, or 600 MHz on *Varian* or *Bruker* instruments with the solvent resonance of $CDCl_3$ (7.26 ppm for ^1H, 77.0 ppm for ^{13}C), acetone-d_6 (2.04 ppm for ^1H, 29.8 ppm for ^{13}C) and methanol-d_4 (3.35 ppm for ^1H, 49.0 ppm for ^{13}C). Coupling constants (*J*) are reported in Hz and splitting patterns are designated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

Compound **6** was obtained from Alfa Aesar. Compound **7**[13] and **22**[11] were prepared following procedure reported in literature. Both were further dried by vacuum distillation over CaH_2 before use.

(*E*)-2-((1-(5-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-2-hydroxy-3-methoxy-4-methylphenyl)ethyl)amino)ethyl propionate (8)

A flame-dried Schlenk flask was charged with a solution of aldehyde **4** (236 mg, 0.57 mmol) in dry Et_2O (6 mL). Methylmagnesium chloride (0.23 mL, 0.60 mmol, 2.6 M solution in THF, 1.05 equiv) was added to the mixture at -78 °C. The mixture was allowed to stir at the same temperature for 10 minutes before adding solution of **6** (1.14 mL, 0.2 mmol, 1.0 M in toluene, 2 equiv.). The mixture was allowed to warm to room temperature over 16 hours. The solution was quenched with saturated NaHCO3 solution (3 mL), extracted with Et_2O (3 × 5 mL). Organic layers were combined, washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 5:1→1:1) to afford pure **8** as yellow oil (198 mg, 80% isolated yield).

TLC: R_f = 0.1 (hexanes/ethyl acetate = 3:1).

^1H NMR ($CDCl_3$, 600 MHz): δ = 6.29 (s, 1H), 5.48 (t, *J* = 5.9 Hz, 1H), 5.10 (t, *J* = 6.8 Hz, 1H), 4.43 (d, *J* = 6.6 Hz, 2H), 4.30-4.25 (m, 1H), 4.12 (ddd, *J* = 11.3, 7.1, 3.8 Hz, 1H), 3.90 (q, *J* = 6.6 Hz, 1H), 3.83 (s, 3H), 2.93-2.82 (m, 2H), 2.37 (q, *J* = 7.7 Hz, 2H), 2.14 (s, 3H), 2.13-2.04 (m, 4H), 1.70 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.16 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 174.3, 150.0, 146.9, 144.0, 140.2, 131.7, 123.9, 123.3, 120.6, 120.3, 107.7, 66.3, 62.9, 60.1, 58.7, 45.9, 39.5, 30.3, 27.4, 26.4, 25.7, 22.2, 17.7, 16.6, 9.1.

6-(1-(Benzylamino)ethyl)-4-(benzyloxy)-2-methoxy-3-methylphenol (9)

A flame-dried Schlenk tube was charged with a solution of **5** (93 mg, 0.25 mmol) and **7** (0.28 mL, 0.28 mmol, 1.0 M in toluene, 1.1 equiv) in dry Et_2O (3 mL). Methylmagnesium chloride (0.1 mL, 0.27 mmol, 2.6 M solution in THF, 1.05 equiv) was added to the mixture at -78 °C. The mixture was allowed to warm to room temperature over 16 hours. The solution was quenched with saturated $NaHCO_3$ solution (3 mL), extracted with Et_2O (3 × 3 mL). Organic layers were combined, washed with brine (3 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was taken up in methanol (3 mL). $TsOH{\cdot}H_2O$ (2.4 mg, 0.013 mmol, 5 mol%) was added. The solution was stirred at room for 10 hours. The reaction was quenched with Et_3N (0.1 mL). The mixture was concentrated, then purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 5:1→1:1) to afford pure product as yellow oil (62.5 mg, 66% isolated yield).

TLC: R_f = 0.2 (hexanes/ethyl acetate = 3:1).

^1H NMR ($CDCl_3$, 600 MHz): δ = 7.45 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.34-7.27 (m, 6H), 6.41 (s, 1H), 5.00 (s, 2H), 3.96 (q, *J* = 6.3 Hz, 1H), 3.87 (s, 3H), 3.84 (d, *J* = 13.2 Hz, 1H), 3.67 (d, *J* = 13.2 Hz, 1H), 2.22 (s, 3H), 1.47 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 149.7, 147.0, 144.4, 138.4, 137.7, 128.6, 128.4, 128.4, 127.6, 127.4, 127.2, 123.6, 120.4, 107.6, 71.1, 60.1, 58.5, 51.5, 22.3, 9.1.

(*E*)-5-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-2-(2-hydroxyethyl)-7-methoxy-3,6-dimethylisoindolin-1-one (Mariline B, 2)

Phenol **8** (130 mg, 0.3 mmol) was dissolved in a biphasic mixture of dichloromethane (3 mL) and aqueous 2 M NaOH solution (1.5 mL). Tetrabutylammonium hydroxide (15.6 mg, 10 mol%, 50% solution in water) and bis(trifluoromethanesulfonyl)aniline (161 mg, 0.45 mmol, 1.5 equiv) were added. The mixture was stirred at room temperature for 16 hours. The mixture was diluted with more dichloromethane (6 mL). The aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 5:1→3:1) to afford **10** as yellow oil (56.0 mg, 33% isolated yield). The product was dissolved in toluene (1.5 mL) in a Schlenk tube under nitrogen atmosphere. To this solution was added tri-*n*-propylamine (28.0 mg, 0.20 mmol, 2.0 equiv), $Pd(OAc)_2$ (2.2

mg, 0.0099 mmol, 10 mol%) and 1,3-bis(diphenylphosphino)propane (4.2 mg, 0.0099 mmol, 10 mol%). The solution was purged with a balloon of carbon monoxide gas for 3 minutes, after which the balloon was left attached to the Schlenk tube. The solution was heated at 100 °C for 16 hours. After cooling to room temperature, the mixture was diluted with ethyl acetate (3 mL) and water (3 mL). Aqueous layer was extracted with ethyl acetate (3 × 3 mL). The organic layers were combined, washed with brine (3 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was taken up in methanol (3 mL), potassium carbonate (41.5 mg, 0.30 mmol, 3 equiv) was added. The suspension was stirred for 2 hours, after which the suspension was filtered. The filtrate collected was concentrated and purified by column chromatography (SiO_2, eluent: DCM/MeOH = 20:1→10:1) to afford **2** as yellow oil (24.4 mg, 64% isolated yield).

TLC: R_f = 0.5 (DCM/MeOH=10:1).

^{1}H NMR (acetone-d_6, 500 MHz): δ = 6.91 (s, 1H), 5.51 (t, *J* = 6.0 Hz, 1H), 5.10 (t, *J* = 6.6 Hz, 1H), 4.72-4.65 (m, 2H), 4.62 (q, *J* = 6.8 Hz, 1H), 3.99 (s, 3H), 3.84 (dt, *J* = 14.2, 5.3 Hz, 1H), 3.71 (m, 2H), 3.34 (ddd, *J* = 14.1, 6.6, 5.1 Hz, 1H), 2.79 (br s, 1H), 2.17-2.10 (m, 4H), 2.09 (s, 3H), 1.76 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H), 1.44 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (acetone-d_6, 126 MHz): δ = 167.4, 161.8, 157.0, 150.0, 141.5, 132.1, 124.7, 120.7, 119.4, 116.3, 101.8, 66.3, 62.2, 61.7, 57.0, 43.7, 40.1, 27.0, 25.8, 19.0, 17.7, 16.7, 8.8.

5-Hydroxy-7-methoxy-3,6-dimethylisoindolin-1-one (Mariline C, 3)

Phenol **9** (56.6 mg, 0.15 mmol) was dissolved in a biphasic mixture of dichloromethane (2 mL) and aqueous 2 M NaOH solution (1 mL). Tetrabutylammonium hydroxide (7.8 mg, 10 mol%, 50% solution in water) and bis(trifluoromethanesulfonyl)aniline (80.5 mg, 0.225 mmol, 1.5 equiv) were added. The mixture was stirred at room temperature for 16 hours. The mixture was diluted with more dichloromethane (3 mL). The aqueous layer was extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 5:1→3:1) to afford **11** as yellow oil (29.0 mg, 38% isolated yield). The product was dissolved in toluene (1 mL) in a Schlenk tube under nitrogen atmosphere. To this solution was added tri-*n*-propylamine (16.3 mg, 0.11 mmol, 2.0 equiv), $Pd(OAc)_2$ (1.3 mg, 0.0057 mmol, 10 mol%) and 1,3-bis(diphenylphosphino)propane (2.4 mg, 0.0057 mmol, 10 mol%). The solution was purged with a balloon of carbon monoxide gas for 3 minutes, after which the balloon was left attached to the Schlenk tube. The solution was heated at 100 °C for 16 hours. After cooling to room temperature, the mixture was filtered through a short silica gel column. The column was washed with EtOAc (3 × 2 mL). The filtrate was concentrated *in vacuo*. The residue was taken up in methanol (2 mL). After adding Pd/C (5.0 mg), the mixture stirred under hydrogen atmosphere for 20 hours. The mixture was filtered through a pad of Celite, after which the filtrate was concentrated. The residue was dissolved in anisole (0.2 mL). Triflic acid (65 mg, 0.57 mmol, 10 equiv) was added. The mixture was heated at 150°C for 48 hours. After cooling to room temperature, the reaction was quenched with Et_3N (0.7 mL) then concentrated. The residue was purified by column chromatography (SiO_2, eluent: DCM/MeOH = 20:1→10:1) to afford **3** as white solid (6.5 mg, 55% isolated yield).

TLC: R_f = 0.2 (DCM/MeOH=10:1).

^{1}H NMR (methanol-d_4, 500 MHz): δ = 6.64 (s, 1H), 4.48 (q, *J* = 6.7 Hz, 1H), 3.91 (s, 3H), 2.11 (s, 3H), 1.38 ppm (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (methanol-d_4, 101 MHz): δ = 171.6, 162.3, 158.4, 152.1, 118.9, 115.0, 105.0, 62.5, 53.2, 20.8, 8.5.

Funding Information

The authors are grateful for financial support from both the UCSB Department of Chemistry & Biochemistry as well as the Faculty Senate.

Acknowledgment

The authors are appreciative of the financial support provided by the Faculty Senate, the Dean of the College of Letters and Science, and the Department of Chemistry and Biochemistry at the University of California, Santa Barbara. In addition, the PI is grateful for the tutelage of his past undergraduate research mentor, Tomás Hudlicky, a provocateur, who strove to prevent solvent contamination of ^{1}H-NMR spectra, to guarantee melting point for solids, to ensure accurate product yields and to educate the ignorant, such as himself.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO.

Conflict of Interest

The authors declare no conflict of interest.

References

(1) Almeida, C.; Hemberger, Y.; Schmitt, S. M.; Bouhired, S.; Natesan, L.; Kehraus, S.; Dimas, K.; Gütschow, M.; Bringmann, G.; König, G. M. *Chem. Eur. J.* **2012**, *18*, 8827-8834.
(2) Augner, D.; Schmalz, H-G. *Synlett* **2015**, 26, 1395-1397.
(3) Min, C.; Lin, Y.; Seidel, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 15353-15357.
(4) (a) Almeida, C.; Bills, G.; GonzAalez-Menésez, V.; Martin, J.; Tormo, J. R.; Genilloud, O. *Fermentation* **2017**, *3*, 45. (b) Schmalz, H. *Preprints* **2019**, 2019110051 (doi: 10.20944/preprints 201911.0051.v1) (c) Madddah, F. E.; Eguereva, E.; Kehraus, S.; König, G. M. *Org. Biomol. Chem.* **2019**, *17*, 2747–2752.
(5) For selected reviews on the applications of *ortho*-quinone methides in total synthesis, see: (a) Willis, N. J.; Bray, C. D. *Eur. J. Chem.* **2012**, *18* (30), 9160-9173. (b) Bai, W.-J.; David, J. G.; Feng, Z.-G.; Weaver, M. G.; Wu, K.L.; Pettus, T. R. R. *Acc. Chem. Res.* **2014**, *47*, 3655–3664. (c) Singh, M. S.; Nagaraju, A.; Anand, N.; Chowdhury, S. *RSC Adv.* **2014**, *4* (99), 55924-55959. (d) Yang, B.; Gao, S. *Chem. Soc. Rev.* **2018**, *47* (21), 7926-7953.
(6) (a) Chan, K. KC, Wong, Y. F.; Yang, D.; Pettus, T. R. R. *Org. Lett.,* **2019**, *21*, 7746-7749. (b) Wong, Y. F.; Hernandez, I. Pettus, T. R. R. *J. Org. Chem.* **2023**, *88*, 2583–2588
(7) (a) Barnard, C. F. J. *Organometallics* **2008**, *27* (21), 5402–5422. (b) Brennführer, A.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133.
(8) Sonesson, C.; Barf, T.; Nilsson. J.; Dijkstra, D.; Carlsson, A.; Svensson, K.; Smith, M. W.; Martin, I. J.; Ducan, N. J.; King, L. J.; Wikström, H. *J. Med. Chem.* **1995**, *38*, 1319-1329.
(9) (a) Crisp, G. T.; Meyer, A. G. *Tetrahedron* **1995**, *51*, 5585-5596. (b) Crisp, G. T.; Meyer, A. G *J. Org. Chem.* **1992**, 52, 6972-6975. (c) Masui, R.; Ohmori, K.; Hintermann, L.; Yoshida, S.; Suzuki, K. *Angew. Chem. Int. Ed.* **2009**, **48**, 3462-3465.
(10) Parker, K. A.; Petraitis, J. J. *Tetrahedron Lett.* **1981**, *22*, 397-400.
(11) Ouyang, J.; Su, X.; Chen, Y.; Yuan, Y.; Li, Y. *Tetrahedron Lett.* **2016**, *57*, 1438–1441
(12) Jones, R. M.; Van De Water, R. W.; Lindsey, C. C.; Hoarau, C.; Ung, T.; Pettus, T. R. R. *J. Org. Chem.* **2001**, *66*, 3435-3441.
(13) Lawson, J. R.; Wilkins, L. C.; Melen, R. L.; *Chem. Eur. J.* **2017**, *23*, 10997-11000.
(14) Wong, Y. F. Conjugate Additions of sp^2 Hybridized Nitrogen Nucleophiles to *ortho*-Quinone Methides. Ph.D. Thesis, University of California, Santa Barbara, CA, 2022.

Checklist (have these on hand for manuscript submission in ScholarOne):

- cover letter, including a statement of the work's significance
- full mailing address, telephone number, and e-mail address of the corresponding author
- email address for each author
- original Word file
- original graphics files zipped into one zip file
- eye-catching graphical abstract as an individual file
- 5–8 key words
- separate Supporting Information file
- Zenodo DOI for optional deposited Primary Data

Useful links:

- SYNTHESIS homepage
- SYNTHESIS information and tools for authors
- Graphical abstract samples (PDF file download)
- What is "Primary Data"?
- ScholarOne (manuscript submission)

*Supporting Information for "***Synthesis of Naturally Racemic Marilines B-C through Multi-Component Reactions Involving *o*-QMs and Various Nitrogen Nucleophiles**"

Yuk Fai Wong, Thomas R. R. Pettus *
Pettus@chem.ucsb.edu

Department of Chemistry and Biochemistry, University of California, Santa Barbara
Santa Barbara, California 93106-9510 (United States)

Table of Contents

1. General Information

In reactions where water was not present as a solvent, reagent, or byproduct, the glassware was flame dried, and the reactions were carried out under an inert atmosphere of nitrogen. Reactions were monitored by analytical thin-layer chromatography on EMD silica gel 60 F254 plates; visualization was effected by ultraviolet light (254 nm), *p*-anisaldehyde or potassium permanganate stains. Solvents were removed using a rotary evaporator.

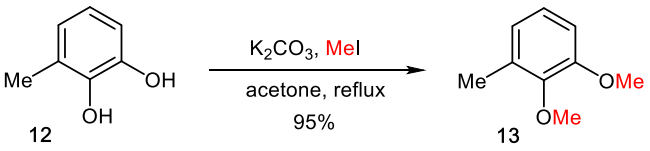
All purchased chemicals were used without purification unless otherwise stated. Dihydrooxazole **6** was obtained from Alfa Aesar. Imine **7**[1] and aniline **22**[2] were prepared following procedure reported in literature. All nitrogen nucleophiles were further dried by vacuum distillation over CaH_2 before use. Dichloromethane was distilled from CaH_2. Benzene, diethyl ether, tetrahydrofuran, and toluene were distilled from sodium and benzophenone. Deuterated chloroform was stored over anhydrous potassium carbonate and 4Å molecular sieves before use.

NMR spectra were recorded at 400, 500, or 600 MHz on *Varian* or *Bruker* instruments with the solvent resonance of $CDCl_3$ (7.26 ppm for ^1H, 77.0 ppm for ^{13}C), acetone-d_6 (2.04 ppm for ^1H, 29.8 ppm for ^{13}C) and methanol-d_4 (3.35 ppm for ^1H, 49.0 ppm for ^{13}C). Coupling constants (J) are reported in Hz and splitting patterns are designated using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad).

[1] Lawson, J. R.; Wilkins, L. C.; Melen, R. L.; *Chem. Eur. J.* **2017**, *23*, 10997-11000.

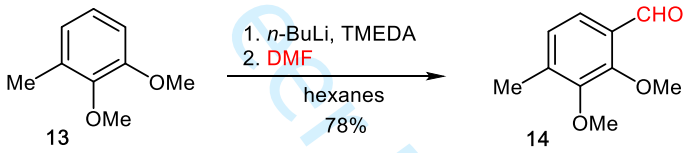
[2] Ouyang, J.; Su, X.; Chen, Y.; Yuan, Y.; Li, Y. *Tetrahedron Lett.* **2016**, *57*, 1438–1441.

2. Syntheses of salicylaldehyde precursors



1,2-Dimethoxy-3-methylbenzene (13)

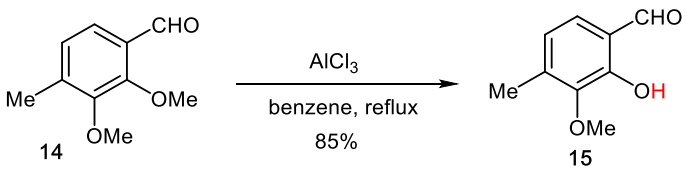
To a solution of 3-methylcatechol **12** (5.00 g, 40 mmol) in acetone (40 mL) was added K_2CO_3 (19.0 g, 136 mmol, 3.4 equiv.), followed by methyl iodide (22.9 g, 160 mmol, 4.0 equiv.). The mixture was allowed to reflux for 48 hours. Upon completion, the mixture was filtered. The filtrate collected was concentrated *in vacuo*, and was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 10:1) to afford pure product as colorless oil (6.03 g, 95% isolated yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 6.95 (t, *J* = 7.9 Hz, 1H), 6.79-6.73 (m, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 2.28 (s, 3H). **R_f** = 0.7 (hexanes/ethyl acetate = 3:1). Our characterization data match with prior literature data.[3]



2,3-Dimethoxy-4-methylbenzaldehyde (14)

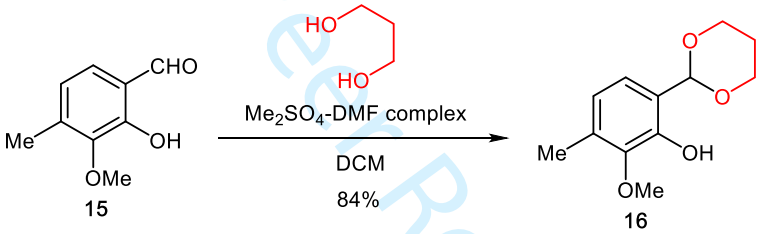
A flame-dried round bottom flask was charged with a solution of **13** (6.00 g, 39 mmol) and TMEDA (1.15 g, 9.75 mmol, 0.25 equiv) in hexanes (150 mL). *n*-BuLi solution (40 mL, 1.2 M solution in pentane, 46.8 mmol, 1.2 equiv) was added over 30 minutes at room temperature. The resulting suspension was stirred at room temperature for 24 hours before cooling to 0 ºC. DMF (5.79 g, 78 mmol, 2.0 equiv) was added dropwise. The solution was allowed to warm to room temperature and stirred for 1 hour. The reaction was then quenched with water (5 mL), followed by addition of 2 M HCl solution until pH of aqueous layer was close to 7. Aqueous layer was extracted with Et_2O (3 × 250 mL). Organic layers were combined, washed with brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 9:1) to afford pure product as yellow oil (5.48 g, 78% isolated yield). **^{1}H NMR** (500 MHz, $CDCl_3$): δ 10.33 (s, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.00 (dt, *J* = 8.0, 0.8 Hz, 1H), 4.00 (s, 3H), 3.86 (s, 3H), 2.32 (s, 3H). **R_f** = 0.3 (hexanes/ethyl acetate = 9:1). Our characterization data match with prior literature data.[3]

[3] Movahhed, S.; Westphal, J.; Kempa, A.; Schumacher, C. E.; Sperlich, J.; Neudörfl, J.; Teusch, N.; Hochgürtel, M.; Schmalz, H. *Eur. J. Chem.* **2021**, *27* (45), 11574-11579.



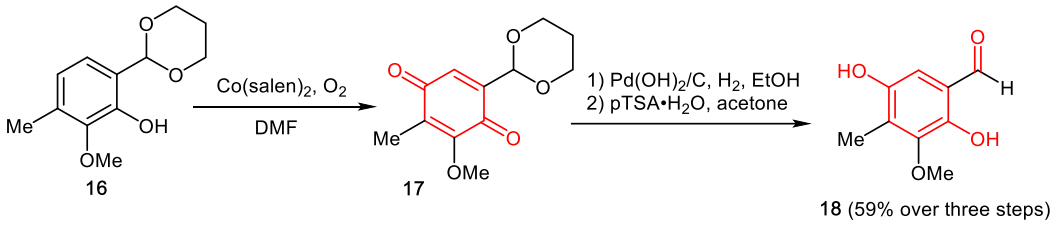
2-Hydroxy-3-methoxy-4-methylbenzaldehyde (15)

To a solution of **14** (6.99 g, 38.8 mmol) in benzene (60 mL) was added $AlCl_3$ (6.21 g, 46.6 mmol, 1.2 equiv) in two portions. The suspension was refluxed for 30 minutes. After cooling to room temperature, the reaction was quenched with aqueous 1 M $NaHSO_4$ solution (50 mL). The biphasic mixture was allowed to stir at room temperature until all solid dissolved. The aqueous layer was extracted with Et_2O (3 × 50 mL). The organic layers were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 20:1) to afford pure product as yellow oil (5.48 g, 85% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 11.15 (s, 1H), 9.83 (s, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 3.90 (s, 3H), 2.33 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 196.0, 154.7, 146.1, 140.9, 128.1, 121.8, 120.3, 60.0, 16.8. **R_f** = 0.3 (hexanes/ethyl acetate = 9:1).



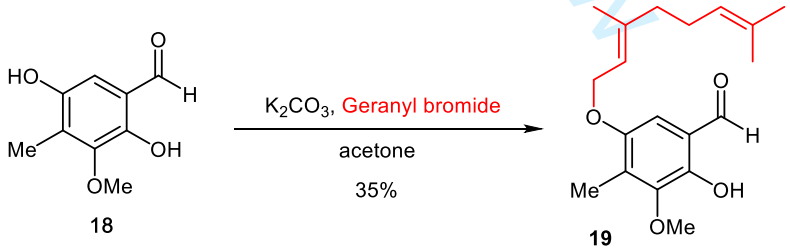
6-(1,3-Dioxan-2-yl)-2-methoxy-3-methylphenol (16)

To a Schlenk flask charged with DMF (6.28 g, 86 mmol) was added dimethyl sulfate (10.84g, 86 mmol) dropwise at 50 ºC. The mixture was then stirred at 80 ºC for 2 hours to obtain DMF-DMS complex. To a separate flask charged with a solution of **15** (6.10 g, 36 mmol) in DCM (20 mL) was added 1,3-propanediol (8 mL), followed by the DMF-DMS complex prepared above. The mixture was allowed to stir at room temperature for 24 hours. The reaction was quenched by slow addition of Et_3N (6 mL) at 0 ºC. The viscous diol layer was extracted with Et_2O (3 × 30 mL). The organic layers were combined, washed with NaOAc saturated $NaHSO_3$ solution (20 mL), followed by NaOAc saturated NaCl solution (20 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 3:1, with 1% Et_3N by volume) to afford pure product as orange oil (6.78 g, 84% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.92 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 5.67 (s, 1H), 4.31-4.26 (m, 2H), 4.04-3.97 (m, 2H), 3.82 (s, 3H), 2.25 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$): δ 147.8, 146.2, 132.5, 122.2, 121.7, 121.5, 101.5, 67.5, 60.2, 46.1, 25.7, 15.9. **R_f** = 0.3 (hexanes/ethyl acetate = 3:1).



2,5-Dihydroxy-3-methoxy-4-methylbenzaldehyde (18)

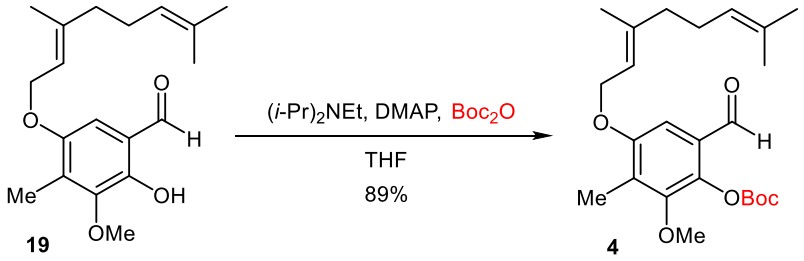
To a solution of **16** (6.23 g, 27.8 mmol) in DMF (100 mL) was added $Co(salen)_2$ (578 mg, 1.7 mmol, 6 mol %). The solution was first saturated with oxygen gas, then an oxygen balloon was connected to the flask. The solution was allowed to stir at room temperature for 48 hours. Upon completion, the solution was diluted with water (300 mL) and Et_2O (300 mL). The aqueous layer was extracted with more Et_2O (3 × 200 mL). The organic layers were combined, washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated to afford the crude *p*-quinone **17**. This crude quinone was re-dissolved in ethyl acetate (130 mL), to which $Pd(OH)_2/C$ (360 mg) was added. A hydrogen balloon was connected, and the suspension was allowed to stir at room temperature for 18 hours. The mixture was then filtered through Celite pad. The filtrate was concentrated *in vacuo* to afford the crude hydroquinone, which was taken up in a mixture of acetone (90 mL) and water (5 mL) immediately. TsOH monohydrate (252 mg, 2.8 mmol, 10 mol %) was added. The mixture was allowed to stir at room temperature for 24 hours. The solution was quenched with Et_3N (1 mL) and concentrated. The residue was extracted with ethyl acetate (4 × 50 mL). The organic layers were combined, washed with brine (40 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 3:1) to afford pure product as brown solid (2.99 g, 59% isolated yield over 3 steps). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 10.70 (s, 1 H), 9.76 (s, 1H), 6.73 (s, 1H), 3.89 (s, 3H), 2.25 (s, 3H). **R_f** = 0.6 (hexanes/ethyl acetate = 1:1).



(*E*)-5-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-2-hydroxy-3-methoxy-4-methylbenzaldehyde (19)

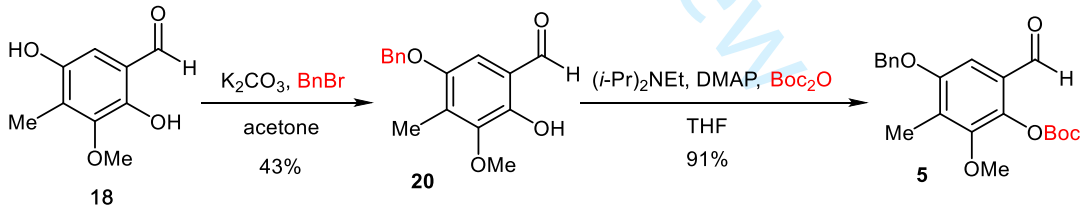
To a solution of **18** (608 mg, 3.34 mmol) in acetone (20 mL) was added K_2CO_3 (923 mg, 6.68 mmol, 2.0 equiv), followed by geranyl bromide (871 mg, 4.01 mmol, 1.2 equiv). The mixture was stirred at room temperature for 24 hours, after which it was filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 30:1) to afford pure product as yellow oil (372 mg, 35% isolated yield). **^{1}H**

NMR (600 MHz, $CDCl_3$): δ 10.27 (s, 1H), 7.02 (s, 1H), 5.50 (td, *J* = 7.4, 1.2 Hz, 1H), 5.31 (br s, 1H), 5.08-5.04 (m, 1H), 4.61 (d, *J* = 7.7 Hz, 2H), 3.88 (s, 3H), 2.22 (s, 3H), 2.11-2.00 (m, 4H), 1.67 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H). $\mathbf{R_f}$ = 0.3 (hexanes/ethyl acetate = 9:1).



(*E*)-*Tert*-butyl (4-((3,7-dimethylocta-2,6-dien-1-yl)oxy)-6-formyl-2-methoxy-3-methylphenyl) carbonate (4)

To a solution of **19** (372 mg, 1.17 mmol) and Hünig's base (75.0 mg, 0.58 mmol, 0.5 equiv) in DCM (20 mL) was added DMAP (4.3 mg, 0.035 mmol, 3 mol%), followed by Boc_2O (255 mg, 1.17 mmol, 1.0 equiv). The solution was stirred at room temperature for 16 hours. The reaction was quenched with water (5 mL). The aqueous layer was extracted with DCM (3 × 10 mL). Organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 30:1) to afford pure product as yellow oil (436 mg, 89% isolated yield). ^{1}**H NMR** (600 MHz, $CDCl_3$): δ 10.13 (s, 1H), 7.08 (s, 1H), 5.46 (td, *J* = 6.5, 1.0 Hz, 1H), 5.12-5.05 (m, 1H), 4.58 (d, *J* = 6.5 Hz, 2H), 3.81 (s, 3H), 2.22 (s, 3H), 2.16-2.04 (m, 4H), 1.74 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H), 1.57 (s, 9H). ^{13}**C NMR** (126 MHz, $CDCl_3$): δ 188.0, 155.6, 151.4, 151.2, 141.4, 140.7, 131.8, 129.6, 126.5, 123.7, 119.1, 105.0, 84.3, 65.7, 61.1, 39.5, 27.6, 26.3, 25.7, 17.7, 16.7, 10.1. $\mathbf{R_f}$ = 0.4 (hexanes/ethyl acetate = 9:1).

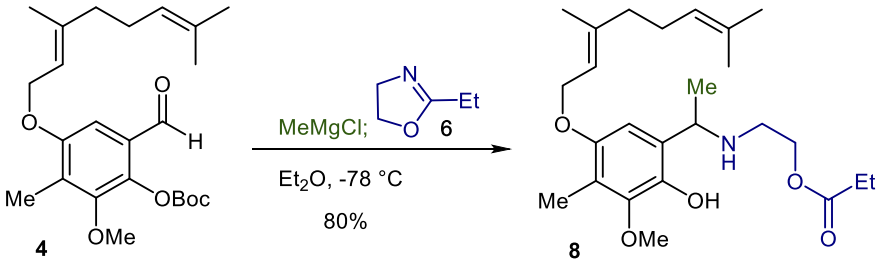


4-(Benzyloxy)-6-formyl-2-methoxy-3-methylphenyl *tert*-butyl carbonate (5)

To a solution of **18** (273 mg, 1.50 mmol) in acetone (10 mL) was added K_2CO_3 (415 mg, 3.00 mmol, 2.0 equiv), followed by benzyl bromide (308 mg, 1.80 mmol, 1.2 equiv). The mixture was stirred at room temperature for 24 hours, after which it was filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 10:1) to give afford pure product as yellow oil (176 mg, 43% isolated yield). The product was dissolved in DCM (10 mL). Hünig's base (41.7 mg, 0.32 mmol, 0.5 equiv), DMAP (2.4 mg, 0.019 mmol, 3 mol%) and Boc_2O (142 mg, 0.65 mmol, 1.0 equiv) were added. The solution was stirred at room temperature for 16 hours. The reaction was quenched with water

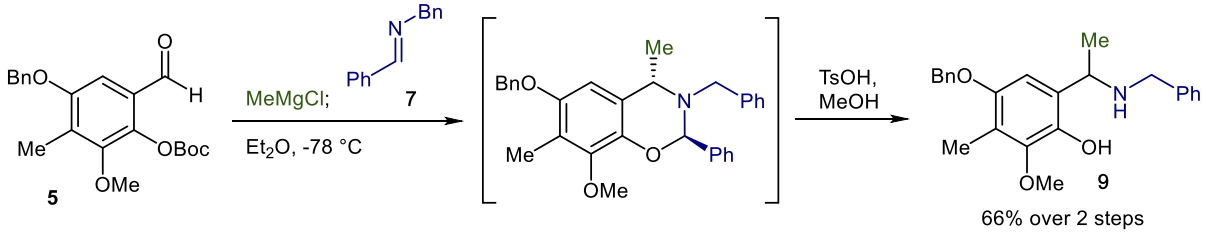
(3 mL). The aqueous layer was extracted with DCM (3 × 5 mL). Organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 5:1) to afford pure product as yellow oil (219 mg, 91% isolated yield). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.14 (s, 1H), 7.47-7.29 (m, 5H), 7.17 (s, 1H), 5.11 (s, 2H), 3.83 (s, 3H), 2.28 (s, 3H), 1.57 (s, 9H). **R_f** = 0.6 (hexanes/ethyl acetate = 3:1).

3. Syntheses of marlines B-C using MCR



(*E*)-2-((1-(5-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-2-hydroxy-3-methoxy-4-methylphenyl)ethyl)amino)ethyl propionate (8)

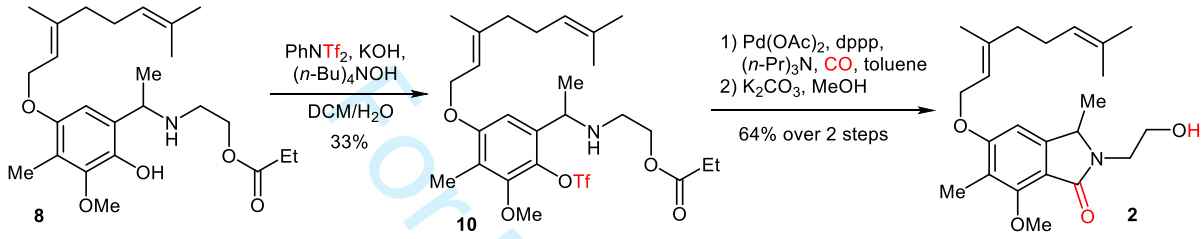
A flame-dried Schlenk flask was charged with a solution of aldehyde **4** (236 mg, 0.57 mmol) in dry Et_2O (6 mL). Methylmagnesium chloride (0.23 mL, 0.60 mmol, 2.6 M solution in THF, 1.05 equiv) was added to the mixture at -78 °C. The mixture was allowed to stir at the same temperature for 10 minutes before adding solution of **6** (1.14 mL, 0.2 mmol, 1.0 M in toluene, 2 equiv.). The mixture was allowed to warm to room temperature over 16 hours. The solution was quenched with saturated $NaHCO_3$ solution (3 mL), extracted with Et_2O (3 × 5 mL). Organic layers were combined, washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 5:1→1:1) to afford pure **8** as yellow oil (198 mg, 80% isolated yield). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 6.29 (s, 1H), 5.48 (t, *J* = 5.9 Hz, 1H), 5.10 (t, *J* = 6.8 Hz, 1H), 4.43 (d, *J* = 6.6 Hz, 2H), 4.30-4.25 (m, 1H), 4.12 (ddd, *J* = 11.3, 7.1, 3.8 Hz, 1H), 3.90 (q, *J* = 6.6 Hz, 1H), 3.83 (s, 3H), 2.93-2.82 (m, 2H), 2.37 (q, *J* = 7.7 Hz, 2H), 2.14 (s, 3H), 2.13-2.04 (m, 4H), 1.70 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.47 (d, *J* = 6.6 Hz, 3H), 1.16 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 126 MHz) δ 174.3, 150.0, 146.9, 144.0, 140.2, 131.7, 123.9, 123.3, 120.6, 120.3, 107.7, 66.3, 62.9, 60.1, 58.7, 45.9, 39.5, 30.3, 27.4, 26.4, 25.7, 22.2, 17.7, 16.6, 9.1. **R_f** = 0.1 (hexanes/ethyl acetate = 3:1).



6-(1-(Benzylamino)ethyl)-4-(benzyloxy)-2-methoxy-3-methylphenol (9)

A flame-dried Schlenk tube was charged with a solution of **5** (93 mg, 0.25 mmol) and **7** (0.28 mL, 0.28 mmol, 1.0 M in toluene, 1.1 equiv) in dry Et_2O (3 mL). Methylmagnesium chloride (0.1 mL, 0.27 mmol, 2.6 M solution in THF, 1.05 equiv) was added to the mixture at -78 °C. The mixture was allowed to warm to room temperature over 16 hours. The solution was quenched with saturated $NaHCO_3$ solution (3 mL), extracted with Et_2O (3 × 3 mL). Organic layers were combined, washed with brine (3 mL), dried over anhydrous Na_2SO_4, and concentrated. The

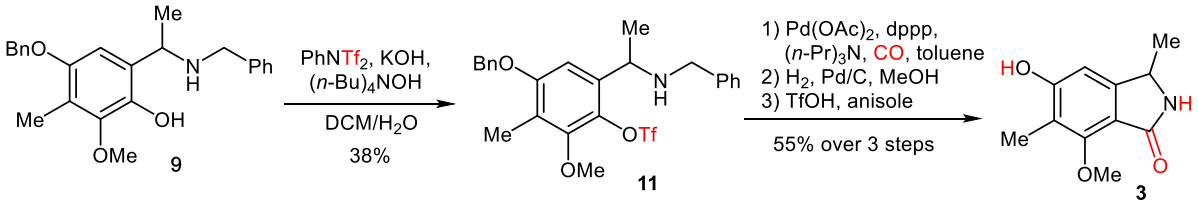
residue was taken up in methanol (3 mL). $TsOH{\cdot}H_2O$ (2.4 mg, 0.013 mmol, 5 mol %) was added. The solution was stirred at room for 10 hours. The reaction was quenched with Et_3N (0.1 mL). The mixture was concentrated, then purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 5:1→1:1) to afford pure product as yellow oil (62.5 mg, 66% isolated yield). **^{1}H NMR** ($CDCl_3$, 600 MHz): δ 7.45 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.34-7.27 (m, 6H), 6.41 (s, 1H), 5.00 (s, 2H), 3.96 (q, *J* = 6.3 Hz, 1H), 3.87 (s, 3H), 3.84 (d, *J* = 13.2 Hz, 1H), 3.67 (d, *J* = 13.2 Hz, 1H), 2.22 (s, 3H), 1.47 (d, *J* = 6.6 Hz, 3H). **^{13}C NMR** ($CDCl_3$, 126 MHz): δ 149.7, 147.0, 144.4, 138.4, 137.7, 128.6, 128.4, 128.4, 127.6, 127.4, 127.2, 123.6, 120.4, 107.6, 71.1, 60.1, 58.5, 51.5, 22.3, 9.1. **R_f** = 0.2 (hexanes/ethyl acetate = 3:1).



(*E*)-5-((3,7-Dimethylocta-2,6-dien-1-yl)oxy)-2-(2-hydroxyethyl)-7-methoxy-3,6-dimethylisoindolin-1-one (Mariline B, 2)

Phenol **8** (130 mg, 0.3 mmol) was dissolved in a biphasic mixture of dichloromethane (3 mL) and aqueous 2 M NaOH solution (1.5 mL). Tetrabutylammonium hydroxide (15.6 mg, 10 mol %, 50% solution in water) and bis(trifluoromethanesulfonyl)aniline (161 mg, 0.45 mmol, 1.5 equiv) were added. The mixture was stirred at room temperature for 16 hours. The mixture was diluted with more dichloromethane (6 mL). The aqueous layer was extracted with dichloromethane (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 5:1→3:1) to afford **10** as yellow oil (56.0 mg, 33% isolated yield). The product was dissolved in toluene (1.5 mL) in a Schlenk tube under nitrogen atmosphere. To this solution was added tri-*n*-propylamine (28.0 mg, 0.20 mmol, 2.0 equiv), $Pd(OAc)_2$ (2.2 mg, 0.0099 mmol, 10 mol %) and 1,3-bis(diphenylphosphino)propane (4.2 mg, 0.0099 mmol, 10 mol %). The solution was purged with carbon monoxide gas for 3 minutes, after which a carbon dioxide gas balloon was left attached to the Schlenk tube. The solution was heated at 100 °C for 16 hours. After cooling to room temperature, the mixture was diluted with ethyl acetate (3 mL) and water (3 mL). Aqueous layer was extracted with ethyl acetate (3 × 3 mL). The organic layers were combined, washed with brine (3 mL), dried over anhydrous Na_2SO_4, and concentrated. The residue was taken up in methanol (3 mL), potassium carbonate (41.5 mg, 0.30 mmol, 3 equiv) was added. The suspension was stirred for 2 hours, after which the suspension was filtered. The filtrate collected was concentrated and purified by column chromatography (SiO_2, eluent: DCM/MeOH = 20:1→10:1) to afford **2** as yellow oil (24.4 mg, 64% isolated yield). **^{1}H NMR** (acetone-d_6, 500 MHz): δ 6.91 (s, 1H), 5.51 (t, *J* = 6.0 Hz, 1H), 5.10 (t, *J* = 6.6 Hz, 1H), 4.72-4.65 (m, 2H), 4.62 (q, *J* = 6.8

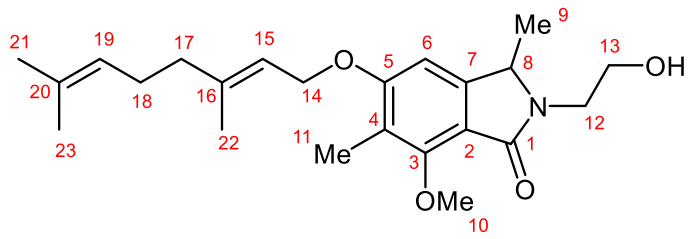
Hz, 1H), 3.99 (s, 3H), 3.84 (dt, *J* = 14.2, 5.3 Hz, 1H), 3.71 (m, 2H), 3.34 (ddd, *J* = 14.1, 6.6, 5.1 Hz, 1H), 2.79 (br s, 1H), 2.17-2.10 (m, 4H), 2.09 (s, 3H), 1.76 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H), 1.44 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (acetone-d_6, 126 MHz): δ 167.4, 161.8, 157.0, 150.0, 141.5, 132.1, 124.7, 120.7, 119.4, 116.3, 101.8, 66.3, 62.2, 61.7, 57.0, 43.7, 40.1, 27.0, 25.8, 19.0, 17.7, 16.7, 8.8. **R_f** = 0.5 (DCM/MeOH = 10:1).



5-Hydroxy-7-methoxy-3,6-dimethylisoindolin-1-one (Mariline C, 3)

Phenol **9** (56.6 mg, 0.15 mmol) was dissolved in a biphasic mixture of dichloromethane (2 mL) and aqueous 2 M NaOH solution (1 mL). Tetrabutylammonium hydroxide (7.8 mg, 10 mol %, 50% solution in water) and bis(trifluoromethanesulfonyl)aniline (80.5 mg, 0.225 mmol, 1.5 equiv) were added. The mixture was stirred at room temperature for 16 hours. The mixture was diluted with more dichloromethane (3 mL). The aqueous layer was extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (SiO_2, eluent: hexanes/ethyl acetate = 5:1→3:1) to afford **11** as yellow oil (29.0 mg, 38% isolated yield). The product was dissolved in toluene (1 mL) in a Schlenk tube under nitrogen atmosphere. To this solution was added tri-*n*-propylamine (16.3 mg, 0.11 mmol, 2.0 equiv), $Pd(OAc)_2$ (1.3 mg, 0.0057 mmol, 10 mol %) and 1,3-bis(diphenylphosphino)propane (2.4 mg, 0.0057 mmol, 10 mol %). The solution was purged with carbon monoxide gas for 3 minutes, after which the carbon dioxide gas balloon was left attached to the Schlenk tube. The solution was heated at 100 °C for 16 hours. After cooling to room temperature, the mixture was filtered through a short silica gel column. The column was washed with EtOAc (3 × 2 mL). The filtrate was concentrated *in vacuo*. The residue was taken up in methanol (2 mL). After adding 10% Pd/C (5.0 mg), the mixture stirred under hydrogen atmosphere for 20 hours. The mixture was filtered through a pad of Celite, after which the filtrate was concentrated. The residue was dissolved in anisole (0.2 mL). Triflic acid (65 mg, 0.57 mmol, 10 equiv) was added. The mixture was heated at 150°C for 48 hours. After cooling to room temperature, the reaction was quenched with Et_3N (0.7 mL) then concentrated. The residue was purified by column chromatography (SiO_2, eluent: DCM/MeOH = 20:1→10:1) to afford **3** as white solid (6.5 mg, 55% isolated yield). **^{1}H NMR** (methanol-d_4, 500 MHz): δ 6.64 (s, 1H), 4.48 (q, *J* = 6.7 Hz, 1H), 3.91 (s, 3H), 2.11 (s, 3H), 1.38 ppm (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (methanol-d_4, 101 MHz): δ 171.6, 162.3, 158.4, 152.1, 118.9, 115.0, 105.0, 62.5, 53.2, 20.8, 8.5. **R_f** = 0.5 (DCM/MeOH = 10:1).

4. Comparison between Synthetic and Natural Marilines B and C

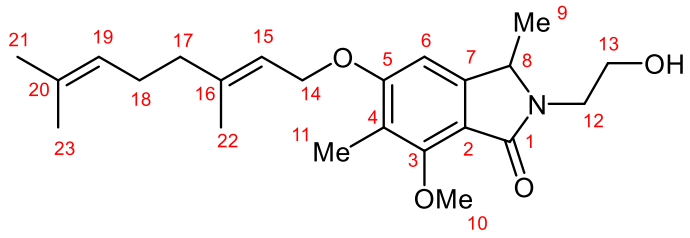


Mariline B (**2**)

Table S1. ^{1}H NMR comparison for mariline B (2).

Assignment[4]	Synthetic Mariline B (acetone-d_6, 500 MHz)	Natural Mariline B[4] (acetone-d_6, 300 MHz)
6	6.91 (s)	6.92 (s)
8	4.62 (q, *J* = 6.8 Hz)	4.62 (q, *J* = 6.8 Hz)
9	1.44 (d, *J* = 6.7 Hz)	1.44 (d, *J* = 6.8 Hz)
10	3.99 (s)	3.98 (s)
11	2.09 (s)	2.09 (s)
12	a: 3.34 (ddd, *J* = 14.1, 6.6, 5.1 Hz) b: 3.84 (dt, *J* = 14.2, 5.3 Hz)	a: 3.33 (dt, *J* = 14.0, 5.5 Hz) b: 3.85 (dt, *J* = 14.0, 5.5 Hz)
13	3.71 (m)	3.71 (m)
14	4.72-4.65 (m)	a: 4.65 (dd, *J* = 12.3, 6.6 Hz) b: 4.71 (dd, *J* = 12.3, 6.6 Hz)
15	5.51 (t, *J* = 6.0 Hz)	5.51 (t, *J* = 6.6 Hz)
17	2.17-2.10 (m)	2.12 (m)
18		2.14 (m)
19	5.10 (t, *J* = 6.6 Hz)	5.10 (t, *J* = 6.6 Hz)
21	1.64 (s)	1.63 (br s)
22	1.76 (s)	1.76 (br s)
23	1.59 (s)	1.58 (br s)

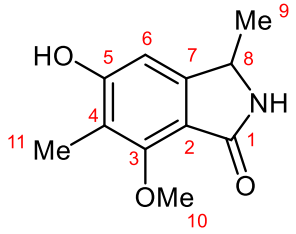
[4] Almeida, C.; Hemberger, Y.; Schmitt, S. M.; Bouhired, S.; Natesan, L.; Kehraus, S.; Dimas, K.; Gütschow, M.; Bringmann, G.; König, G. M. *Chem. Eur. J.* **2012**, *18*, 8827-8834.



Mariline B (**2**)

Table S2. ^{13}C NMR comparison for mariline B (2).

Assignment[4]	Synthetic Mariline B (acetone-d_6, 126 MHz)	Natural Mariline B[4] (acetone-d_6, 75 MHz)
1	167.4	167.3
2	116.3	116.3
3	157.0	156.9
4	119.4	119.3
5	161.8	161.7
6	101.8	101.8
7	150.0	150.0
8	57.0	56.9
9	19.0	18.9
10	62.2	62.1
11	8.8	8.8
12	43.7	43.6
13	61.7	61.7
14	66.3	66.2
15	120.7	120.6
16	141.5	141.5
17	40.1	40.1
18	27.0	27.0
19	124.7	124.6
20	132.1	132.1
21	25.8	25.8
22	16.7	16.7
23	17.7	17.7



Mariline C (**3**)

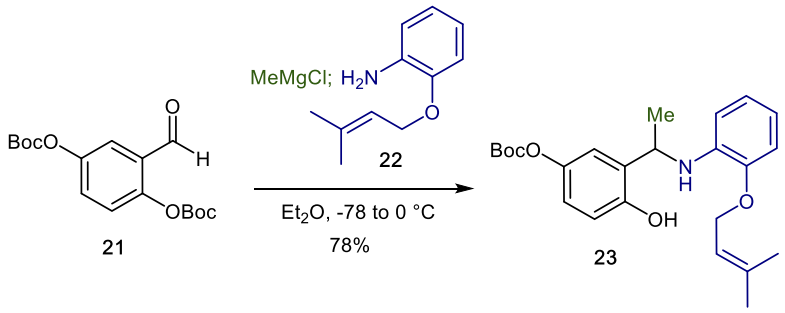
Table S3. ^{1}H NMR comparison for mariline C (3).

Assignment[4]	Synthetic Mariline C (methanol-d_4, 500 MHz)	Natural Mariline C[4] (methanol-d_4, 300 MHz)
6	6.64 (s)	6.68 (s)
8	4.48 (q, J = 6.7 Hz)	4.53 (q, J = 6.8 Hz)
9	1.38 (d, J = 6.7 Hz)	1.42 (d, J = 6.8 Hz)
10	3.91 (s)	3.95 (s)
11	2.11 (s)	2.15 (s)

Table S4. ^{13}C NMR comparison for mariline C (3).

Assignment[4]	Synthetic Mariline C (methanol-d_4, 101 MHz)	Natural Mariline C[4] (methanol-d_4, 75 MHz)
1	171.6	171.7
2	115.0	114.5
3	158.4	158.4
4	118.9	118.9
5	162.3	162.3
6	105.0	105.0
7	152.1	152.1
8	53.2	53.2
9	20.8	20.8
10	62.5	62.5
11	8.5	8.6

5. Studies on the synthesis of mariline A



***Tert*-butyl (4-hydroxy-3-(1-((2-((3-methylbut-2-en-1-yl)oxy)phenyl)amino)ethyl)phenyl) carbonate (23)**

To a flame-dried Schlenk tube was charged with a solution of **21** (33.8 mg, 0.1 mmol) in dry Et_2O (1 mL). Methylmagnesium chloride (0.04 mL, 0.105 mmol, 2.6M solution in THF, 1.05 equiv) was added to the mixture at -78 ºC. The mixture was allowed to stir at the same temperature for 10 minutes before addition of **22** solution (0.11 mL, 0.11 mmol, 1.0 M in toluene, 1.1 equiv.). The mixture was allowed to warm to room temperature over 16 hours. The solution was quenched with saturated $NaHCO_3$ solution (1 mL), extracted with Et_2O (3 × 1 mL). Organic layers were combined, washed with brine (1 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography (SiO_2: eluent: hexanes/ethyl acetate = 10:1→3:1) to afford pure product as orange oil (32.4 mg, 78% isolated yield). **^{1}H NMR** (600 MHz, $CDCl_3$): δ 6.99-6.95 (m, 2H), 6.86-6.74 (m, 5H), 5.52-5.45 (m, 1H), 4.60-4.51 (m, 2H), 4.44 (q, *J* = 6.8 Hz, 1H), 1.81 (s, 3H), 1.74 (s, 3H), 1.61 (d, *J* = 6.7 Hz, 3H), 1.56 (s, 9H). **R_f** = 0.1 (hexanes/ethyl acetate = 9:1).

6. NMR Spectra