Toward a Total Synthesis of Divergolide A; Synthesis of the Amido Hydroquinone Core and the C10–C15 Fragment

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Abstract: A ring-closing metathesis (RCM) approach was envisioned for installing the *E* double bond at the C9 and C10 positions of divergolide A, isolated from a mangrove endophyte. Accordingly, the C10–C15 diene diol fragment and the amido hydroquinone core with the requisite functionalities and stereochemistry have been synthesized by using the norephedrine-based *syn*-selective glycolate aldol and the *anti*-selective aldol reactions, respectively. CuI-catalyzed amidation was employed to access the anilide intermediate, which was further transformed into the amido hydroquinone core.

Key words, aldol reactions, selectivity, natural products, hydroquinone, total synthesis

Divergolide A–D were reported recently as the novel ansa macrolides isolated from an endophyte strain (*Streptomyces* sp. HKI0576) of the dominant mangrove tree *Bruguiera gymnorrhiza* found on the Chinese coast.[1] The structures of these four ansa macrolides were elucidated by conventional spectroscopic methods, and the identity of divergolide A (**1**; Scheme 1) was further confirmed by X-ray crystallographic analysis. It was suggested that these ansa macrolides share a macrocyclic intermediate possessing a hydroxy anilide core and a polyketide chain. This intriguing finding suggested a highly divergent biosynthetic pathway, which was an observation that led to the naming of these new compounds. Preliminary antibacterial and cytotoxic activities were undertaken. Divergolide A (**1**) and D (not shown) exhibited the strongest activity against *Mycobacterium vaccae* (*Mv*), and *Bacillius subtilis* (*Bs*) and methicillin-resistant *Staphylococcus aureus* (MRSA), respectively, whereas divergolide D gave IC_{50} values of 1.0–2.0 μM for lung cancer (LXFA 629L), pancreatic cancer (PANC-1), renal cancer (RXF 486L), and sarcoma (Saos-2).[1,2] As a continuation of our work on diverted total synthesis[3] of marine macrolides, such as amphidinolide T1–T5,[4] X,[5b] and Y,[5a] and iriomoteolide-1a stereoisomers,[6] we initiated a research program for the total synthesis of divergolide A–D based on a ring-closing metathesis (RCM)[7] approach. As shown in Scheme 1, divergolide A (**1**) can be derived retrosynthetically from the larger macrocycle **2**. The latter can be further divided into five small fragments **3**–**7** according to RCM at C9–C10, ester cleavage, methyl ketone aldol–oxidation at C3–C4, *anti*-selective aldol at C1–C2,[8] and CuI-catalyzed amidation.[9] Because divergolide A–D share the same C6–C15 polyketide bridge appended on different heteroaromatic motifs, this RCM approach should enable use of the same C10–C15 fragment **5** in the total synthesis of all these ansa macrolides. We report here on the synthesis of the C10–C15 fragment **5** through a *syn*-selective norephedrine glycolate aldol reaction,[10] and on the amido hydroquinone core from the starting materials **6** and **7** (Scheme 1).

The norephedrine glycolate aldol reaction reported by Andrus and co-workers is sensitive to the oxygen protecting group, which might influence chelation of the oxygen atom with boron. Good to excellent diastereomeric ratios (dr > 9:1) were obtained with methyl and benzyl glycolates but not for the silyl analogue.[10] For our purpose, a readily removable protecting group was necessary because the diols at C11 and C12 in **13** (Scheme 2) should be orthogonally protected for synthesis of divergolide A–D. Therefore, we used the PMB-protected chiral glycolate **10** in the synthesis of **13**. Carboxylic acid **9**, prepared from 4-methoxybenzyl alcohol **8**, was condensed with the known (1*R*,2*S*)-norephedrine derivative **16**[8b] (DCC/DMAP) to give **10** in 88% yield. Treatment of the latter with *c*-Hex_2BOTf–Et_3N in CH_2Cl_2 at –78 °C formed the *Z*-boron enolate,[10a] which reacted with aldehyde **17a** to furnish the *syn*-aldol product **11a** in 89% isolated yield.

Unfortunately, the diastereomeric ratio of **11a** was only 63:37, which was consistent with the result reported for the aldol reaction of the same aldehyde using the methyl glycolate.[10a] In contrast, the reaction of **10** with acrolein **17b** gave the *syn*-aldol product **11b** in 97% yield and with a diastereomeric ratio of 89:11. Attempted reductive removal of the norephedrine auxiliary in the silyl ether derived from **11b** using DIBAL-H resulted in the formation of a complex mixture. Thus, the norephedrine-derived ester **11b** was hydrolyzed using LiOH in THF–H_2O and the resultant acid was treated with trimethylsilyldiazomethane ($TMSCHN_2$) to form the corresponding methyl ester

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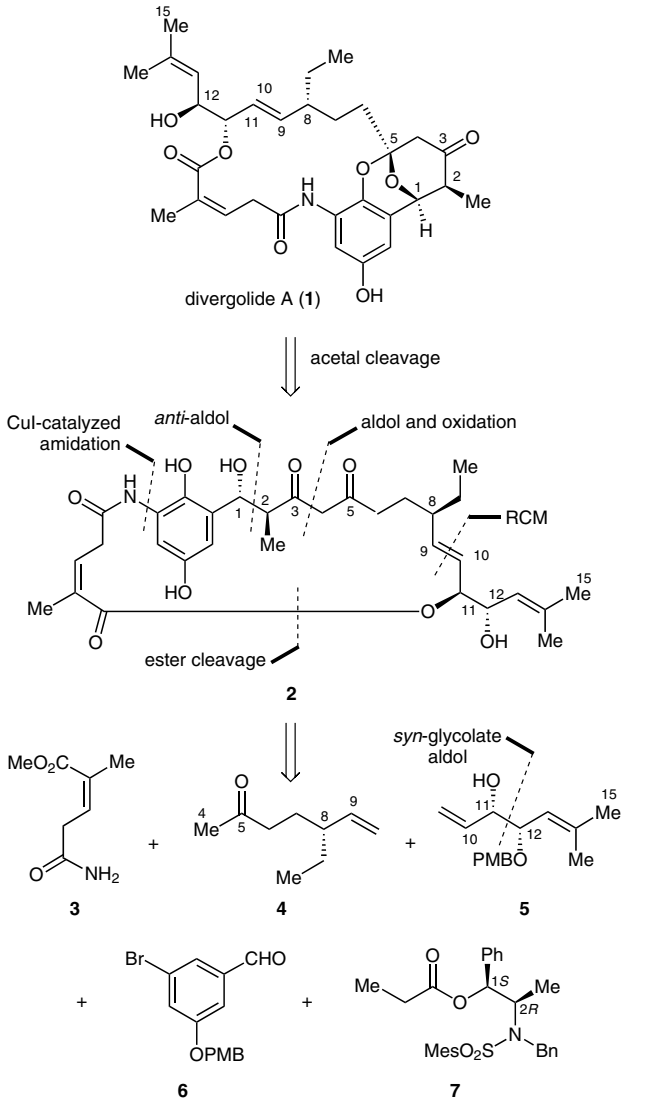
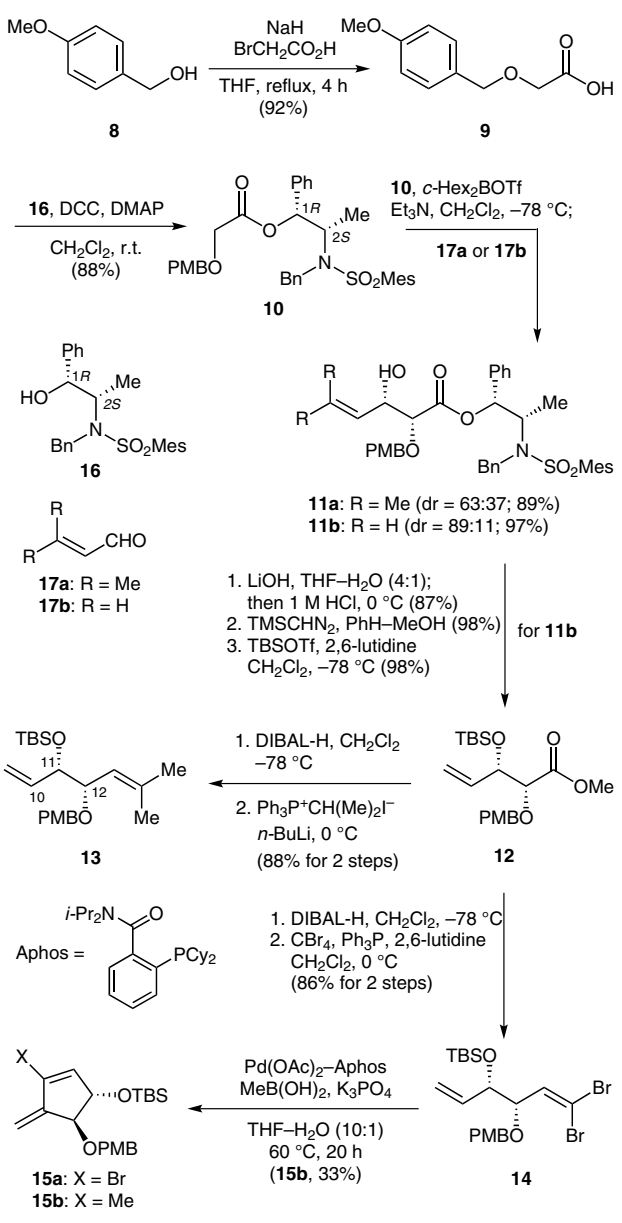


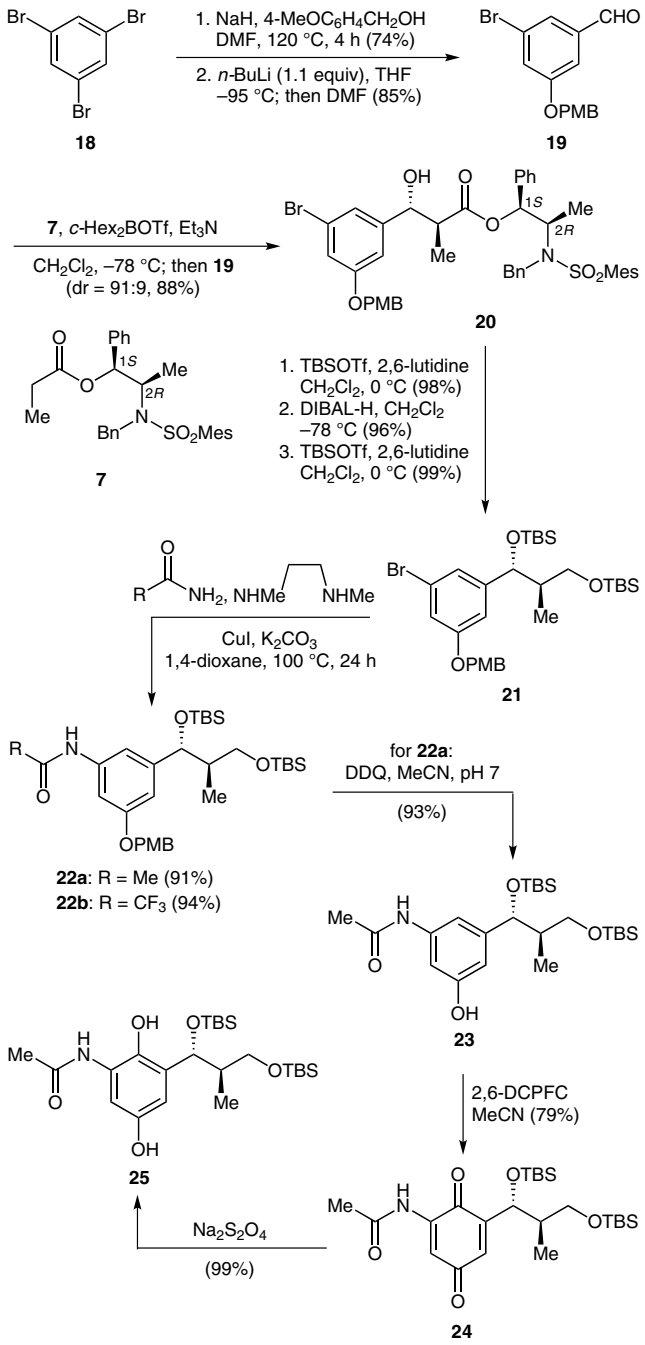
Scheme 1 Retrosynthetic analysis of divergolide A (**1**) based on ring-closing metathesis (RCM) at C9 and C10

in excellent overall yield. The latter was further silylated to furnish the fully protected methyl ester **12**. Partial reduction of **12** using DIBAL-H at –78 °C formed the aldehyde which, without isolation, was transformed into 1,1-dibromoalkene **14** under the Corey–Fuchs conditions[11] in 86% overall yield for the two steps. We attempted to perform double B-alkyl Suzuki–Miyaura cross-coupling of **14** with $MeB(OH)_2$ using our $Pd(OAc)_2$–Aphos catalyst,[12] but, instead of **13**, the unexpected product **15b** was isolated in 33% yield (not optimized). Formation of the cyclopentene derivative **15b** is interesting and might involve an intramolecular Heck reaction to produce the bromo cyclopentene intermediate **15a**, followed by an intermolecular B-alkyl Suzuki–Miyaura cross-coupling of **15a** with $MeB(OH)_2$. We have demonstrated that both types of reactions can be catalyzed by our $Pd(OAc)_2$–Aphos catalyst.[12,13] The target C10–C15 diene diol **13** was finally synthesized by a Wittig reaction of the ylide, $Ph_3P{=}CH(Me)_2$, in 88% overall yield from ester **12** (Scheme 2).[14]

The amido hydroquinone core is the main structural unit unique to divergolide A. We envisioned the 3,5-disubstituted benzaldehyde **19** (Scheme 3) as the precursor, which could be derived from 1,3,5-tribromobenzene **18**. Nucleophilic aromatic substitution of **18** with 4-methoxybenzyl alcohol in the presence of NaH in DMF at 120 °C produced the 3,5-dibromophenyl ether in 74% yield.[15] The latter, upon treatment with *n*-BuLi at –95 °C, was selectively converted into the mono-bromo aryllithium followed by quenching with DMF to furnish the bromobenzaldehyde **19** in 85% yield. An *anti*-selective aldol reaction of the norephedrine propionate **7** with **19** in the presence of *c*-Hex_2BOTf and Et_3N[8] afforded the *anti*-aldol product **20** in 88% yield with a diastereomeric ratio of 91:9. Protection of the hydroxyl group in **20** as the silyl ether, DIBAL-H reduction of the ester moiety, and silylation of the primary alcohol, afforded aryl bro-



Scheme 2 Synthesis of the C10–C15 fragment **13**



Scheme 3 Synthesis of the amido hydroquinone core **25**

mide **21** in excellent overall yield. With **21** in hand, we investigated the metal-catalyzed model amidation reactions; the results are summarized in Table 1. The reaction of acetamide with **21** in the presence of $Pd(OAc)_2$ and BINAP (catalyst A) in toluene at 110 °C for 1.5 hours formed many new components, from which the desired amidation product **22a** was isolated in only 17% yield (Table 1, entry 1).

The same amidation catalyzed by CuI and 1,10-phenanthroline (catalyst B) did not form the product, although the aryl bromide **21** underwent decomposition (Table 1, entry 2). Fortunately, the combination of CuI with *N*,*N*′-dimethylethylenediamine (catalyst C) was found to be efficient for promoting the amidation, however, substrate conversion demonstrated a remarkable solvent dependence (Table 1, entries 3–5). Upon reacting at 110 °C for 24 hours in 1,4-dioxane, the product **22a** was isolated in 91% yield. Similarly, the reaction of **21** with trifluoroacetamide furnished the product **22b** in 94% yield (Table 1, entry 6).

Table 1 Pd- or Cu-Catalyzed Amidation of **21**[a]

Entry	Cat.[b]	Base	Solvent	Time (h)	Product	Yield (%)[c]
1	A	K_2CO_3	toluene	1.5	**22a**	17[d]
2	B	K_3PO_4	DMF	20[e]	**22a**	trace
3	C	K_2CO_3	toluene	24	**22a**	22[f]
4	C	K_2CO_3	1,4-dioxane	17	**22a**	71[g]
5	C	K_2CO_3	1,4-dioxane	24	**22a**	91
6	C	K_2CO_3	1,4-dioxane	24	**22b**	94

[a] The reaction was carried out at 110 °C in the given base (3 equiv), solvent, and catalyst.
[b] Catalyst A: $Pd(OAc)_2$ (3 mol%) and BINAP (5 mol%); Catalyst B: CuI (5 mol%) and 1,10-phenanthroline (10 mol%); Catalyst C: CuI (5 mol%) and *N*,*N*′-dimethylethylenediamine (10 mol%).
[c] Isolated yield.
[d] Many spots were observed by TLC analysis of the reaction.
[e] Reaction performed at 120 °C.
[f] With recovery of **21** in 65% yield.
[g] With recovery of **21** in 24% yield.

Cleavage of the PMB ether in **22a** by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave amido phenol **23** in 93% yield. Oxidation of **23** to quinone **24** was examined using a variety of oxidants[16] and the results are summarized in Table 2. All oxidants failed in the oxidation except for 2,6-dicarboxypyridinium fluorochromate (2,6-DCPFC), which was prepared from 2,6-dicarboxypyridine, 40% aqueous HF, and CrO_3.[17] Treatment of the amido phenol **23** with 2,6-DCPFC for 1 min at room temperature afforded the amido quinone **24** in 79% isolated yield (Scheme 3 and Table 2, entry 9).[18] Finally, reduction of **24** using $Na_2S_2O_4$ furnished the model amido hydroquinone core **25** in 99% yield.[19]

In summary, we have synthesized the C10–C15 diene *syn*-diol fragment and the amido hydroquinone core appended with the C1–C3 *anti*-aldol subunit. The norephedrine-based *syn*-selective glycolate aldol[10] and the *anti*-selective aldol[8] reactions were used to secure four among the five stereogenic centers in divergolide A (**1**). Moreover, the CuI-catalyzed amidation reaction was utilized for installation of the anilide intermediate. The latter was then transformed into the amido hydroquinone core through 2,6-DCPFC-mediated oxidation of the *meta*-amidophenol. The results described above should lay down a firm foundation for advancement of our total synthesis of divergolide A based on the proposed ring-closing metathesis strategy.

Table 2 Selected Results for the Oxidation of **23** to Amido Quinone **24**

Entry	[O][a]	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	CAN	MeCN–H_2O	20	3	NR
2	DDQ	CH_2Cl_2–H_2O	20	3	NR
3	IBX	CH_2Cl_2	20	3	NR
4	$K_2S_2O_8$	THF–H_2O	0	10 (min)	NR
5	CrO_3	CH_2Cl_2–H_2O	0	5 (min)	NR
6	$KMnO_4$	THF–H_2O	20	1	NR
7	BTI	MeCN–H_2O	0	3	NR
8	PbO_2	DMF	20	5	NR
9	2,6-DCPFC	MeCN	20	1 (min)	79

[a] Oxidants [O]: CAN = cerium(IV) ammonium nitrate; IBX = 2-iodoxybenzoic acid; BTI = [bis(trifluoroacetato)iodo]benzene; 2,6-DCPFC = 2,6-dicarboxypyridinium fluorochromate.
[b] Isolated yield. NR = no reaction.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(14) **Synthesis of Diene 13 from Ester 12:** To a solution of **12** (285.4 mg, 0.75 mmol) in anhydrous CH_2Cl_2 (8 mL) cooled in a dry ice–acetone bath (–78 °C) under an N_2 atmosphere was added slowly a solution of DIBAL-H (1 M in toluene, 1.1 mL, 1.1 mmol). The resultant mixture was stirred for 1.5 h at the same temperature, then MeOH (2 mL) was added to quench the reaction. The reaction mixture was allowed to warm to –40 °C, then a saturated aqueous solution of potassium sodium tartrate was added followed by stirring at r.t. until the mixture became clear. The mixture was extracted with CH_2Cl_2 (5 × 3 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude aldehyde. The latter was dissolved in anhydrous THF (2 mL) for use in the next step without further purification.
To a solution of $Ph_3P^+CH(Me)_2I^-$ (486.3 mg, 1.13 mmol) in anhydrous THF (10 mL) cooled in an ice–water bath (0 °C) under an N_2 atmosphere was added *n*-BuLi (1.5 M in hexane, 0.74 mL, 1.1 mmol) followed by stirring at the same temperature for 30 min. After cooling the resultant solution of the ylide to –78 °C, the above THF solution of the aldehyde was added and the resultant mixture was stirred for 2 h at –78 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl at –78 °C and the reaction mixture was allowed to warm to r.t. and extracted with EtOAc (8 × 3 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2; EtOAc–petroleum ether, 1:120) to give diene **13** (248.6 mg, 88% yield for 2 steps from **12**).
Compound 13: Colorless oil; $[\alpha]_D^{20}$ +3.78 (*c* 1.20, $CHCl_3$); R_f = 0.40 (EtOAc–petroleum ether, 1%); IR (film): 2954, 2925, 2854, 1614, 1514, 1249, 1064, 1039 cm^{-1}. ^1H NMR

(400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 5.87 (ddd, *J* = 16.8, 10.4, 5.2 Hz, 1 H), 5.24 (d, *J* = 17.2 Hz, 1 H), 5.09 (d, *J* = 10.0 Hz, 1 H), 5.07 (d, *J* = 7.6 Hz, 1 H), 4.52 and 4.31 (ABq, *J* = 11.6 Hz, 2 H), 4.17 (dd, *J* = 5.6, 5.2 Hz, 1 H), 3.95 (dd, *J* = 9.6, 6.4 Hz, 1 H), 3.80 (s, 3 H), 1.76 (s, 3 H), 1.59 (s, 3 H), 0.88 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 137.9, 137.4, 131.2, 129.2 (2×), 122.5, 114.9, 113.5 (2×), 78.4, 75.8, 69.4, 55.2, 26.0, 25.9 (3×), 18.7, 18.3, –4.7, –4.8. HRMS (EI+): *m*/*z* [M^+] calcd for $C_{22}H_{36}O_3Si$: 376.2434; found: 376.2433.

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(18) **Synthesis of Quinone 24 via Oxidation of Phenol 23:** To a solution of phenol **23** (257.0 mg, 0.55 mmol) in MeCN (4 mL) at r.t. was quickly added an aqueous solution of 2,6-DCPFC (334 mg in 1.1 mL H_2O, 1.1 mmol), prepared according to the literature procedure.[17a] After stirring for 1 min, the reaction was quenched by addition of saturated aqueous $NaHCO_3$. The reaction mixture was extracted with EtOAc (10 × 3 mL) and the combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2; EtOAc–petroleum ether, 1:40) to give quinone **24** (209.3 mg, 79% yield) as a yellow solid. Mp 80–81 °C (CH_2Cl_2–pentane); $[\alpha]_D^{20}$ +53.60 (*c* 1.10, $CHCl_3$); R_f = 0.40 (EtOAc–petroleum ether, 2.4%). IR (film): 3380, 3296, 2957, 2925, 2854, 1714, 1650, 1606, 1502, 1255, 1099 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.06 (br s, 1 H, NH), 7.50 (d, *J* = 2.8 Hz, 1 H), 6.70 (dd, *J* = 2.0, 1.2 Hz, 1 H), 4.73 (d, *J* = 4.8 Hz, 1 H), 3.57 (dd, *J* = 10.0, 5.6 Hz, 1 H), 3.44 (dd, *J* = 10.0, 5.2 Hz, 1 H), 2.22 (s, 3 H), 1.94–1.91 (m, 1 H), 0.90 (s, 9 H), 0.89 (d, *J* = 6.0 Hz, 3 H), 0.81 (s, 9 H), 0.06 (s, 3 H), –0.05 (s, 3 H), –0.07 (s, 3 H), –0.09 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 188.2, 182.6, 169.1, 148.2, 138.1, 133.3, 114.5, 69.1, 63.5, 42.4, 25.8 (3×), 25.8 (3×), 24.8, 18.3, 18.0, 14.2, –4.6, –5.2, –5.5, –5.6. HRMS (EI+): *m*/*z* [M^+] calcd for $C_{24}H_{43}NO_5Si_2$: 481.2680; found: 481.2682.

(19) **Synthesis of Hydroquinone 25 via Reduction of 24:** To a yellow solution of quinone **24** (144.5 mg, 0.30 mmol) in a mixed solvent of THF–Et_2O–H_2O (6 mL; v/v/v = 1:1:1) at r.t., was added $Na_2S_2O_4$ (525 mg, 3 mmol) in portions with vigorous stirring until the yellow color of the mixture disappeared. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (5 × 3 mL). The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2; EtOAc–petroleum ether, 1:3) to give hydroquinone **25** (145.2 mg, 99% yield) as a colorless oil. R_f = 0.50 (EtOAc–PE, 33%). [Note: Hydroquinone **25** was oxidized to quinone in air during acquisition of ^{13}C NMR data. No optical rotation data was taken for this sample]. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.19 (s, 1 H, NH), 8.10 (s, 1 H, OH), 7.91 (s, 1 H, OH), 7.55 (s, 1 H), 6.32 (s, 1 H), 4.84 (d, *J* = 6.0 Hz, 1 H), 3.61 (dd, *J* = 9.6, 4.4 Hz, 1 H), 3.43 (dd, *J* = 9.2, 7.2 Hz), 2.34 (s, 3 H), 2.15–2.07 (m, 1 H), 0.94 (s, 9 H), 0.89 (s, 9 H), 0.74 (d, *J* = 6.8 Hz, 3 H), 0.11 (s, 3 H), 0.9 (s, 6 H), –0.05 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.3, 149.7, 137.0, 126.9, 126.0, 109.8, 106.2, 64.7, 60.4, 42.4, 25.9 (4×), 25.7 (3×), 24.8, 18.3, 18.1, –5.1, –5.3 (2×), –5.5. HRMS (EI+): *m*/*z* [M^+] calcd for $C_{24}H_{45}NO_5Si_2$: 483.2836; found: 483.2834.