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Synthesis of 12,12′-azo-13,13′-*diepi*-Ritterazine N

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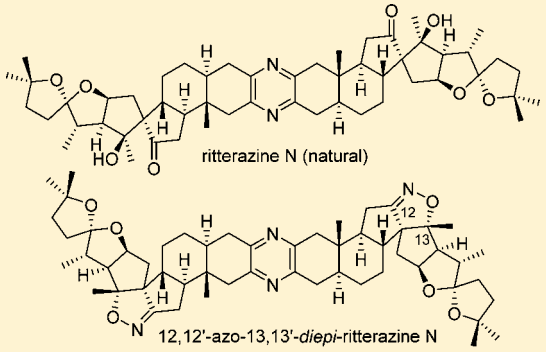
Supporting Information

ABSTRACT: A synthesis of the 12,12′-azo-analogue of ritterazine N from hecogenin is reported. Ring contraction of two 6/5 bicyclic ring systems, one trans-fused and another spiro, to 5/5 spiro ring systems is accomplished with excellent stereochemical control. Key transformations include an abnormal Baeyer−Villiger oxidation, a Norrish type I cleavage, an intramolecular dipolar [3 + 2] cycloaddition, and an intramolecular oxymecuration. Failing to uncover the β-OH ketone from the isoxazoline ring, we end up with a synthesis of a cyclic analogue of ritterazine N.



INTRODUCTION

Ritterazines and cephalostatins form a family of 45 structurally unprecedented trisdecacyclic bissteroidal pyrazines, which induce apoptosis in apoptosis-resistant malignant cells and showed cytotoxicity against human tumors at low nanomolar level.[1] Their unique structures, powerful bioactivities, and scarcity from natural sources have stimulated extensive synthetic endeavors; several members of this family have been synthesized.[2]

Unlike all of the 19 cephalostatins, which contain the standard steroidal core structure, namely, the 6/6/6/5 ABCD ring system, half of the 26 ritterazines, represented by ritterazines N (**1**) and V (**2**) in Figure 1, have a rearranged 6/6/5/5 ABCD ring system featuring a CD spiro ring system connected by a quaternary C14. In 2008, Taber and co-workers reported a total synthesis of 18,18′-desmethyl ritterazine N from nonsteroidal starting materials, which is the only example of constructing this intriguing 6/6/5/5 ring system until now.[3] Our interest lies in facile construction of this ring system, whether it is natural or not, from steroidal precursors. Herein we report our synthetic study toward this attractive structure.

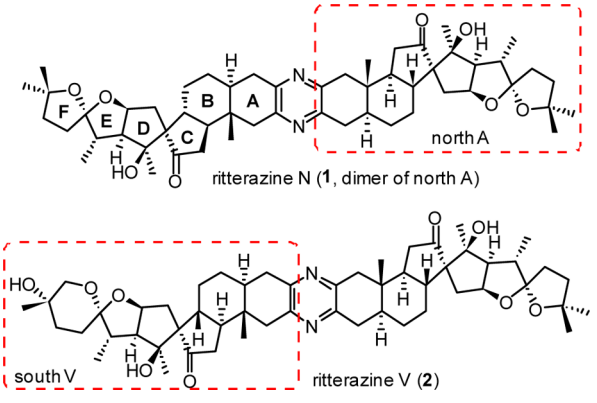
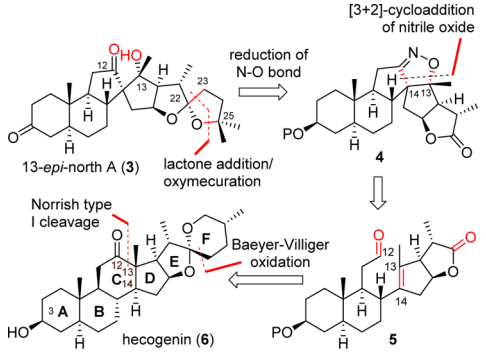


Figure 1. Structures of ritterazines N (**1**) and V (**2**).

RESULTS AND DISCUSSION

North A[2b] is a basic subunit existing in all of the ritterazines that have the rearranged ABCD ring system. We selected 13-*epi*-north A as our target and hecogenin (**6**), a readily available steroidal sapogenin, as the starting material (Scheme 1). Two basic problems are the transformation of the CD rings in **6** from a 6/5 trans-fused bicyclic system to a 5/5 spiro ring system and of the EF rings from a 6/5 spiroketal to a 5/5 spiroketal. Breaking the rings C and F was needed prior to creating new ones, for which we selected Norrish type I

Scheme 1. Retrosynthetic Analysis of 13-*epi*-North A (3), P = *t*-Butyldiphenylsilyl



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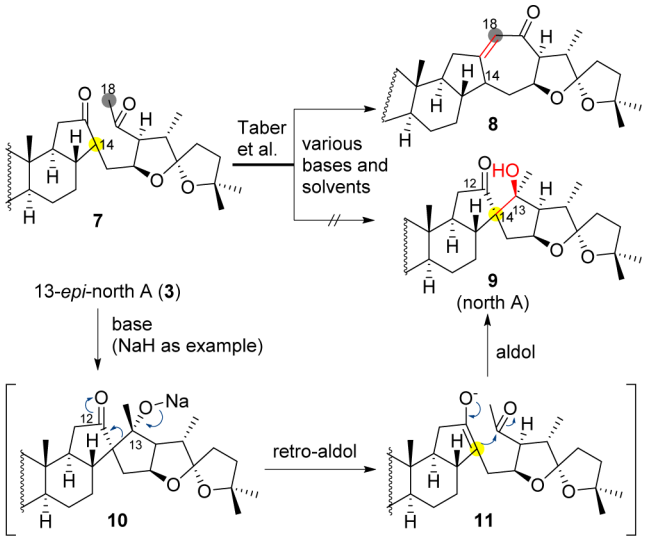
cleavage of the C12 ketone and abnormal Baeyer−Villiger oxidation of the EF rings. The former reaction would open the ring C by cleaving the C12−C13 bond of **6** to give C12 aldehyde and C13−C14 double bond,[4] and the latter would remove the ring F to give a lactone ring E,[2e,5] therefore leading to aldehyde **5**. The desired CD spiro ring was to be constructed via an intramolecular 1,3-dipolar cycloaddition of the C13−C14 double bond and a nitrile oxide derived from C12 aldoxime of **5**, and the 5/5 spiroketal was to be prepared from the lactone ring E of **4** via a nucleophilic addition and oxymecuration, with both the C14 and the C22 configurations being controlled by substrates. As isoxazolines are good precursors for β-hydroxyl ketones,[6] reducing the N—O bond of **4** would introduce C13-OH and C12-ketone, hence providing 13-*epi*-north A (**3**).

Moreover, we anticipated that 13-*epi*-north A (**3**), if needed, could be converted to north A via a retro-aldol/aldol process (Scheme 2).[7] Taber and co-workers showed that intramolecular

Scheme 2. Rationale of Reaching North A from 13-*epi*-North A



aldol reaction of diketone **7** could not construct the desired 5/5 spiro ring system of **9**, but gave predominantly the cycloheptenone **8**.[3c] Clearly, enolizing the C13 ketone at C18 was easier than enolizing the C12 ketone at C14. Triggered by a base, retro-aldol reaction of **3** could form enolate specifically at C14 position, which was necessary for synthesizing north A (**9**) from **7** but unable to achieve otherwise. Therefore, the retro-aldol/aldol process of **3** might give an easy excess to north A.

Our synthesis started from converting **6** to 3,12-dihydroxyl steroidal lactone **12** via an abnormal Baeyer−Villiger oxidation, a process we used in our synthesis of cephalostatin 1[2e] (Scheme 3). The C12 ketone of **6** was reduced with sodium borohydride in methanol/THF to give a mixture of rockogenin (12β-OH) and its 12α-epimer, which was used without purification since the C12 ketone would be reinstalled later. The crude was treated with peracetic acid in the presence of iodine (0.1 equiv) at 50 °C for 5 h and then exposed to KOH in ethanol at reflux to afford **12**, along with a small amount of its 12α-epimer. The C3-OH of **12** was selectively protected as TBDPS ether and the C12-OH was oxidized with Jones reagent to provide ketone **13** in 58% overall yield from **6** on the 100 g scale. About 50% of **13** was harvested via slurry in hexane and 8% via column chromatography on silica gel.

Then ketone **13** was irradiated with 300 W high-pressure mercury lamp in dioxane at ambient temperature for 36−50 h to give **5** in 70% yield on the 10 mmol scale. Unstable in acidic medium, **5** was treated with hydroxylamine hydrochloride and pyridine in ethanol to give a complex mixture, even at −20 °C. We found that neutralization of hydroxylamine hydrochloride with NaOH before reacting with **5** gave better results, providing aldoxime **14** in 66−70% yields. Treated with $PhI(OAc)_2$[8] in DCM at 0 °C, **14** underwent intramolecular dipolar cycloaddition smoothly, giving **4** as a single isomer. We reasoned that the nitrile oxide **15**, generated upon oxidizing **14** with $PhI(OAc)_2$, should approach the C13−C14 double bond from the less hindered, convex face of the cis-fused DE rings, thus forming the desired stereochemistry at C14, which was confirmed later.

As both aldehyde **5** and aldoxime **14** were unstable and difficult to purify, using the crude directly and combining the reactions in one flask was preferred in practice. Therefore, we performed the Norrish cleavage in dioxane, switched the solvent to ethanol, and treated the crude **5** with hydroxylamine and $PhI(OAc)_2$, sequentially. In this manner, **4** was isolated as a single isomer in 42% yield from **13** on the 20 g scale. The first eight steps (from **6** to **4**) needed only two purifications.

With the CD spiro ring system established, we tried to install the 5/5 spiroketal from **4**. Reaction of **4** with (3-methylbut-3-en-1-yl)lithium (prepared via lithium-iodide exchange of 4-iodo-2-methylbut-1-ene **16** with *t*-BuLi in ethyl ether) gave hemiketal **17** in 95% yield. Fuchs and co-workers reported that upon treating in a hot aqueous acetic acid, a substrate with a C25−C26 double bond and a C20−C22 enol ether double bond could cyclize to form 5/5 spiroketal in good yield.[2f] However, submitting **17** to the same conditions did not give **18**. Treated with $Hg(OAc)_2$ in DCM, **17** was converted into intermediate **18**, reduction of which with $NaBH_4$ gave a complex system and delivered **19** in only 30−40% yield. Considering that the complexity might be due to competing reduction of the isoxazoline ring, we investigated weaker reducing reagents. Both $NaBH_3CN$ and $NaBH(OAc)_3$[9] provided cleaner reaction and the latter was better. Without degassing the solvent, reduction of the C—Hg bond of **18** with $NaBH(OAc)_3$ (2 equiv) gave **19** in 66% yield as a single isomer, along with the C26-OH OH product **20**[10] in 26% yield, on the multigram scale. Strict degassing could not eliminate the generation of **20**. The structure of **20** was determined via **21** after removal of the TBDPS ether.

We reasoned that the EF rings of **21**, upon treating with acid, could be transformed partially from to 5/5 spiroketal to 5/6 spiroketal,[11] a structural feature of the south part of ritterazine V (**2**) (south V). However, treatment of **21** with 0.4−1.0 equiv of TsOH in refluxing chloroform for 20 h did not give any noticeable products (Scheme 4). Neither did treatment of **21** with HCl in methanol. The experimental fact proved that 5/5 spiroketal is much more stable than 5/6 spiroketal, such that south V could not be prepared in this way.

With both 5/5 spiro ring systems constructed, we set to explore reductive cleavage of the N—O bond of the isoxazoline ring to reveal the β-OH ketone unit (Scheme 5). Removal of the TBDPS ether of **19** gave **23** in 95% yield. Treatment of **23** with Raney nickel and hydrogen in methanol gave not the desired 13-hydroxyl-12-ketone **24** but diketone **25** in 80% yield, which was presumably generated via a retro-aldol process of the resultant β-OH ketone **24**.[12] As described by Taber and co-workers,[3c] rebuilding the 5/5 spiro ring system from **25** to

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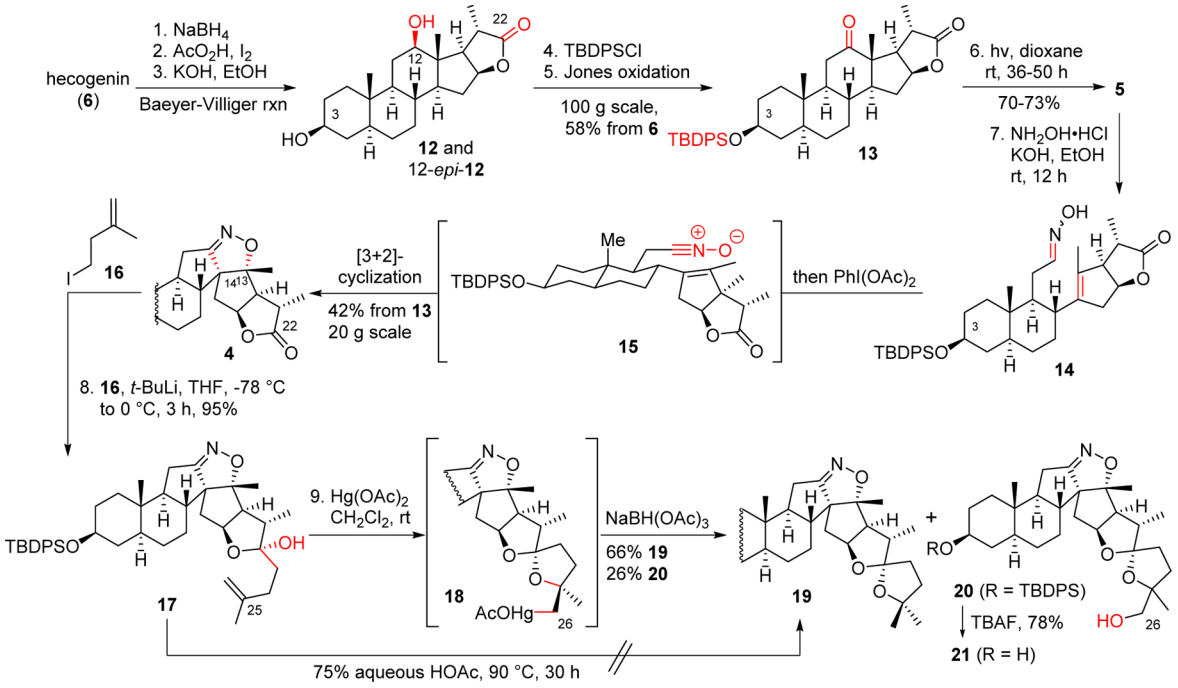
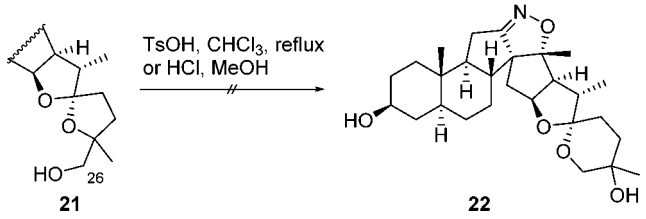
Scheme 3. Construction of Heptacyclic Intermediate 19



Scheme 4. Attempt of Converting 5/5 Spiroketal to 5/6 Spiroketal

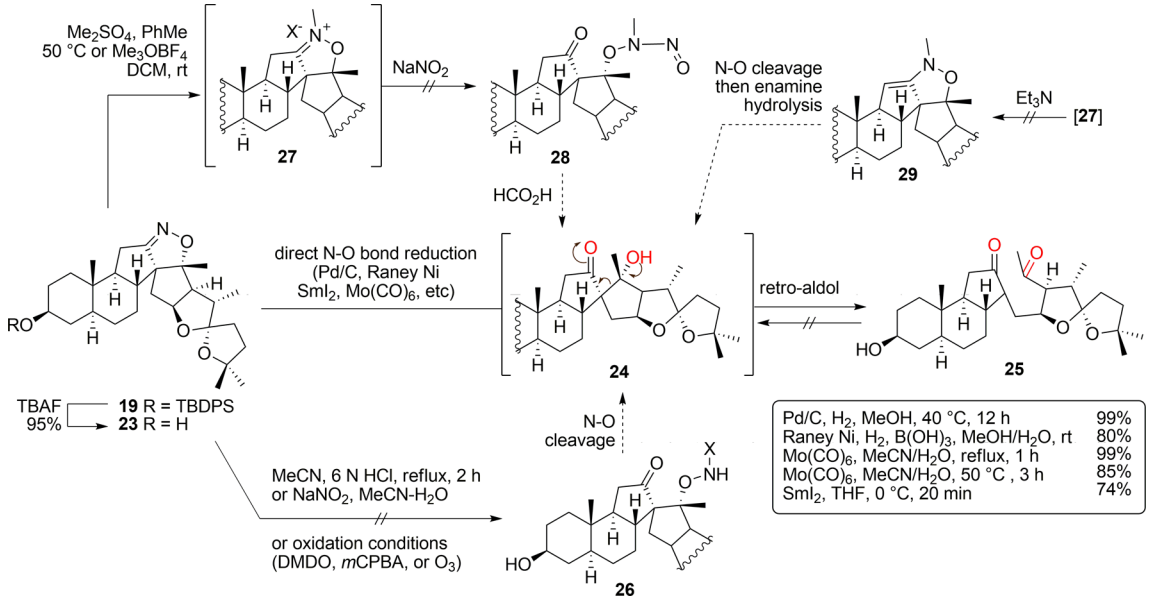


deliver **24** or north A (13-*epi*-**24**) by an intramolecular aldol reaction also failed in our hands.

To stop the reaction at **24**, we buffered the Raney Ni reduction with boric acid, a condition that was reported to inhibit the retro-aldol reactions accompanying the reduction of isoxazolines,[13] only to find no improvement of the outcome. Reduction of **23** with $Mo(CO)_6$[14] gave **25** in high yield, so did reduction with SmI_2 in THF[15] at 0 °C, with Na/Hg in ethanol, and catalytic hydrogenation with Pd/C in methanol.

Our attempts of hydrolyzing the C═N double bond prior to N—O bond cleavage also could not deliver the desired C12 ketone.[16] Since *β*-OH ketone **19** unmasked from isoxazoline tends to undergo retro-aldol reaction, we assumed that **19** could be obtained by hydrolyzing the C═N double bond and then cleaving the N—O bond. Direct hydrolysis of **23** in acidic

Scheme 5. Conditions Failed to Deliver *β*-OH Ketone from Isoxazoline



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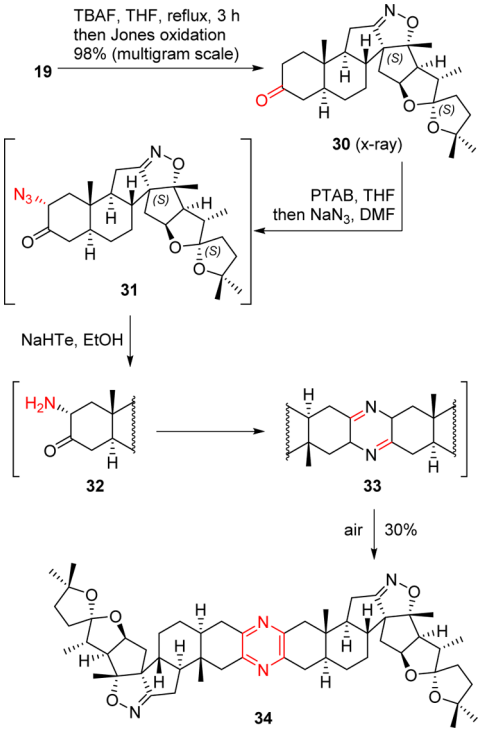
medium, in the presence of $NaNO_2$, or after oxidation[17] with 3-chloroperoxybenzoic acid (*m*CPBA)/ozone (O_3)/dimethyldioxirane (DMDO, prepared in situ by the reaction of acetone with oxone) did not open the isoxazoline ring to give **26**. We tried to increase the electrophilic reactivity of the C═N double bond of **19** by quarternization of the nitrogen atom (Me_2SO_4, toluene, 50 °C; or Me_3OBF_4, CH_2Cl_2, rt); the crude **27** was then reacted with aqueous solutions of H_2O_2, $KMnO_4$, and $NaNO_2$, or treated with Et_3N. We were not able to detect the desired products in the crude reaction mixtures.

Although the functional groups at C12 and C13 are tethered by the N—O bond, **23** resembles north A in structure, which means they might have similar bioactivities. We decided to dimerize **23** to prepare a bissteroidal pyrazine (Scheme 6).

Scheme 6. Synthesis of Dimer 34



Removal of the TBDPS ether of **19** and oxidation of the exposed C3-OH afforded ketone **30** in high yield on the multigram scale. Crystallization of **30** from acetone–hexane gave single crystal suitable for X-ray analysis (CCDC 1505744, see the Supporting Information for the X-ray structure of **30**).[18] Both C14 and C22 of **30** were thus confirmed to be *S*-configured, which were in accordance with the natural ones.

According to a process reported by Suzuki and co-workers,[3c,18] bromination of **30** at C2 using phenyltrimethylammonium tribromide (PTAB) and substitution of the resultant α-bromoketone with sodium azide in DMF gave α-azido ketone **31**, the crude of which was treated with an ethanolic solution of NaHTe at ambient temperature for 1 h, followed by stirring the mixture in air for 12 h, to give the dimer **34** in 30% yield. Reduction of the α-azido ketone **31** with PPh_3, as in the Staudinger reduction, followed by stirring in air could not deliver **34** in our hands.

CONCLUSIONS

In summary, we prepared a cyclic analogue of ritterazine N from hecogenin. The six-membered rings C and F in starting materials were contracted to five-membered spiro rings. The former was realized via a Norrish type I cleavage and a dipolar [3 + 2]-cycloaddition, the latter via an abnormal Baeyer–Villiger oxidation, an addition of the resulting lactone, and an oxymecuration. The stereochemical outcomes of both processes were substrate-controlled. Although we failed to reach the desired 13-*epi*-north A due to the strong tendency of the intermediate to split the ring D via a retro-aldol reaction, our route provided easy access to this unique 6/6/5/5/5/5 ring system. For now, gram scale of **30** and more than 100 mg of **34** are available for any interested collaborators.

EXPERIMENTAL SECTION

General Information. The following procedures were used unless otherwise noted. Moisture-sensitive reactions were carried out in flame-dried glassware sealed under a positive pressure of dry argon. All reagents and solvents were purified and dried according to common methods. Column chromatography was performed on 200–300 mesh silica gel under slightly positive pressure. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on 400 MHz equipment and carbon nuclear magnetic resonance (^{13}C NMR) spectra on 100 MHz equipment. Chemical shifts are reported with solvent resonance as internal standard ($CDCl_3$: δ_H 7.26, δ_C 77.16).

Lactone ***12.*** The preparation of **12** was previously reported (ref 2e) and, as the 12-epimer is also useful, the workup procedures are modified. To a solution of hecogenin **6** (95 g, commercially available, 90% purity, 199 mmol) in THF/MeOH (1000 mL/250 mL) under stirring at 0 °C, was added $NaBH_4$ (5.50 g, 148 mmol) in portions. After stirring for 2 h, the reaction was quenched by addition of HOAc (20 mL) and filtered. After evaporating the organic solvents in vacuo, plenty of water was added and shaken violently to get a good sharp of precipitation. The white solid was collected by filtration, washed with water, and used in the next reaction without further purification. To a suspension of the crude product in HOAc (500 mL) was added H_2SO_4 (9.2 mL, cat.) and iodine (5.20 g, 20 mmol), and the mixture was stirred at ambient temperature for 30 min. The freshly prepared peracetic acid (ca. 1.0 M, 1000 mL) was added in three portions. The temperature of the mixture rose to 60 °C in 1 h and resulted in a dark violet clear solution. If needed, an oil bath at 50 °C for 6 h was employed to drive the oxidation to completion. The reaction was carefully quenched by addition of saturated aqueous Na_2SO_3 solution until the color of iodine faded, and then concentrated in vacuo to remove acetic acid. The residue was filtered and washed with ethanol and concentrated, and then coevaporated with toluene to remove HOAc. The resulting pale yellow oil was used directly without purification. To a solution of the crude product in EtOH (500 mL) KOH (56.0 g, 1.0 mol) was added. The reaction was vigorously stirred at reflux for 5 h and cooled to room temperature. A diluted aqueous HCl solution was added and a copious white solid precipitate (pH < 3). The solid was collected by filtration, washed by hot water, and dried in vacuo overnight. The crude lactone **12** was used in the next step without further purification. **Lactone 12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.91–5.00 (m, 1H), 3.54–3.67 (m, 1H), 3.37 (dd, J = 11.1, 4.8 Hz, 1H), 2.78 (q, J = 7.6 Hz, 1H), 2.24–2.35 (m, 1H), 2.03–2.09 (m, 1H), 1.29 (d, J = 10.8 Hz, 3H), 0.83 (s, 3H), 0.78 (s, 3H).

Preparation of Ketone ***13.*** To a solution of crude **12** in DCM/DMF (400 mL/40 mL) were added DMAP (1.22 g, 10 mmol), imidazole (34.05 g, 500 mmol), and TBDPSCl (53.0 mL, 56.0 g, 204 mmol). After stirring at ambient temperature for 24 h, the reaction was quenched by addition of water. The aqueous layer was extracted with DCM, the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude C12 alcohol was dissolved in DCM/acetone/ether (350 mL/50 mL/350 mL) and treated with Jones reagent under an ice–water bath. Complete consumption of the alcohol was realized after 30 min, and

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the reaction was quenched with saturated aqueous NaOAc solution. The mixture was separated; the aqueous layer was extracted with DCM twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. To the crude solid was added hexane (500 mL), and the resulting slurry was heated to reflux for 30 min and filtered to collect ketone **13** (52.56 g) as a white solid. The filtrate was concentrated, and purified through flash column chromatograhy (PE/EA: 8/1 to 4/1) to give ketone as foam (16.21 g, 68.77 g in total, 57.8% over 5 steps).

C12 Alcohol. Rf: 0.48 (hexane/ethyl acetate: 3/1); $[\alpha]_D^{29}$ − 28 (*c* 1.00, $CHCl_3$); IR (film): 3437, 2932, 2856, 1755, 1472, 1110, 702, 532 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69−7.65 (m, 4H), 7.45−7.33 (m, 6H), 4.95−4.86 (m, 1H), 3.62−3.52 (m, 1H), 3.33−3.25 (m, 1H), 2.75 (q, *J* = 7.6 Hz, 1H), 2.30−2.18 (m, 1H), 2.01 (d, *J* = 7.8 Hz, 1H), 1.32 (d, *J* = 7.7 Hz, 3H), 1.04 (s, 9H), 0.81 (s, 3H), 0.75 (s, 3H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.7 (C), 135.9 (CH), 134.9 (C), 134.9 (C), 129.5 (CH), 127.6 (CH), 82.6 (CH), 79.7 (CH), 72.7 (CH), 58.6 (CH), 53.2 (CH), 53.0 (CH), 46.6 (CH), 44.8 (C), 38.2 (CH), 37.3 (CH), 37.1 (CH), 35.6 (C), 34.0 (CH), 32.8 (CH), 31.9 (CH), 31.7 (CH), 30.7 (CH), 28.5 (CH), 27.1 (CH_3), 19.2 (C), 17.8 (CH_3), 12.4 (CH_3), 8.7 (CH_3); HRMS-MALDI (*m*/*z*): $[M + H]^+$ calcd. for $C_{38}H_{52}SiO_4$: 601.3708, found: 601.3697.

Ketone 13. Rf: 0.78 (hexane/ethyl acetate: 3/1); $[\alpha]_D^{20}$ + 19.7 (*c* 1.00, $CHCl_3$); IR (film): 2931, 2857, 1772, 1713, 1427, 1111, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73−7.63 (m, 4H), 7.49−7.37 (m, 6H), 4.93−4.86 (m, 1H), 3.66−3.55 (m, 1H), 2.65−2.57 (m, 2H), 2.49−2.34 (m, 2H), 2.22 (dd, *J* = 14.4, 5.0 Hz, 1H), 1.41 (d, *J* = 7.6 Hz, 3H), 1.08 (s, 12H), 0.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.8 (C), 180.9 (C), 135.8 (CH), 134.8 (C), 129.6 (CH), 127.6 (CH), 81.0 (CH), 72.4 (CH), 55.8 (CH), 55.8 (CH), 54.2 (CH), 50.9 (CH), 44.6 (CH), 38.1 (CH_2), 37.4 (CH_2), 36.8 (CH), 36.6 (CH_2), 36.2 (C), 34.2 (CH), 32.5 (CH_2), 31.5 (CH_2), 31.5 (CH_2), 28.2 (CH_2), 27.1 (CH_3), 19.2 (C), 17.4 (CH_3), 13.9 (CH_3), 12.1 (CH_3); HRMS-MALDI (*m*/*z*): $[M + Na]^+$ calcd. for $C_{38}H_{50}SiO_4$: 621.3372, found 621.3379.

Preparation of 4 from 13. A solution of ketone **13** (20.12 g, 33.6 mmol) in dioxane (450 mL) was degassed by bubbling with argon for 15 min and then irradiated with 300 W high pressure Hg lamp for 40 h. TLC analysis showed that most of the starting material was consumed. Concentration under reduced pressure gave crude aldehyde **5**, which was dissolved with EtOH (150 mL) and used directly in the next step. To a solution of NaOH (2.05 g, 50 mmol) in EtOH (100 mL) was added hydroxylamine hydrochloride (3.48 g, 50 mmol). The resulting solution was stirred at ambient temperature for 30 min and the above solution of **5** in EtOH was added. The resulting mixture was stirred at ambient temperature for 12 h, and then $PhI(OAc)_2$ (13.26 g, 68 mmol) was added. The mixture was stirred for another 8 h, quenched with a saturated aqueous solution of $Na_2S_2O_3$, and concentrated under reduced pressure. The crude was dissolved with ethyl acetate/ether (200 mL/200 mL), washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. Purification through column chromatography on silica gel (PE/EA: 10/1 to 5/1) gave **4** (8.722 g, 42% from **13**) as a white foam.

Aldehyde 5 (Unstable). Rf: 0.60 (hexane/ethyl acetate: 4/1); $[\alpha]_D^{29}$ − 0.76 (*c* 0.25, $CHCl_3$); IR (film): 3436, 2930, 2856, 1772, 1427, 1181, 1111, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.47 (s, 1H), 7.74−7.61 (m, 4H), 7.45−7.31 (m, 6H), 4.95 (td, *J* = 6.4, 1.4 Hz, 1H), 3.69−3.47 (m, 1H), 1.61 (s, 3H), 1.32 (d, *J* = 7.9 Hz, 1H), 1.04 (s, 9H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.5 (CH), 180.2 (C), 137.4 (C), 135.7 (CH), 134.7 (C), 134.6 (C), 132.1 (C), 129.5 (CH), 129.5 (CH), 127.5 (CH), 127.5 (CH), 80.0 (CH), 72.3 (CH), 57.9 (CH), 45.7 (CH), 43.8 (CH), 43.5 (CH_2), 38.5 (CH), 38.1 (CH_2), 37.8 (C), 37.7 (CH_2), 36.3 (CH), 31.4 (CH_2), 30.8 (CH_2), 28.0 (CH_2), 27.0 ($3CH_3$), 19.1 (C), 17.7 (CH_3), 12.3 (CH_3), 12.2 (CH_3); HRMS-MALDI (*m*/*z*): $[M + Na]^+$ calcd. for $C_{38}H_{50}O_4Si$: 621.3370, found 621.3372.

Aldoxime 14 (mixture of isomers). Rf: 0.42 (hexane/ethyl acetate: 2/1); $[\alpha]_D^{29}$ − 0.44 (*c* 0.75, $CHCl_3$); IR (film): 3373, 2930, 2856, 1771, 1427, 1110, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.64 (m, 4H), 7.45−7.33 (m, 6H), 7.21 (t, *J* = 5.6 Hz, 0.4 Hz, C12−H of one isomer), 6.50 (t, *J* = 5.2 Hz, 0.44 Hz, C12−H of another isomer), 5.07−5.00 (m, 1H), 3.68−3.56 (m, 1H), 2.99−2.91 (m, 1H), 1.65 (s, 3H), 1.36 (d, *J* = 7.2 Hz, 3H), 1.08 (s, 9H), 0.87 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture, for reference only) δ 180.4, 153.7, 153.1, 137.3, 135.9, 134.9, 134.9, 134.8, 129.6, 129.6, 127.6, 127.6, 80.3, 80.2, 72.5, 72.4, 58.1, 49.1, 48.9, 44.2, 38.7, 38.6, 38.3, 38.1, 37.8, 37.5, 37.2, 37.0, 31.6, 31.2, 29.8, 28.9, 28.2, 27.1, 24.9, 19.3, 17.8, 12.3, 12.2, 12.1; HRMS-MALDI (*m*/*z*): $[M + Na]^+$ calcd. for $C_{38}H_{51}NO_4Si$: 636.3479, found 636.3475.

[3 + 2]-Adduct 4. Rf: 0.60 (hexane/ethyl acetate: 1/1); $[\alpha]_D^{29}$ + 12.0 (*c* 1.0, $CHCl_3$); IR (film): 2931, 1777, 1427, 1110, 822, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.64 (m, 4H), 7.45−7.33 (m, 6H), 5.10 (dd, *J* = 13.4, 7.5 Hz, 1H), 3.64−3.54 (m, 1H), 2.84 (dd, *J* = 9.4, 7.0 Hz, 1H), 2.04−2.39 (4H), 1.96 (dd, *J* = 9.8, 5.6 Hz, 1H), 1.84−1.75 (m, 1H), 1.33 (d, *J* = 7.6 Hz, 3H), 1.28 (s, 3H), 1.05 (s, 9H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6 (C), 173.1 (C), 135.9 (CH), 134.8 (C), 134.7 (C), 129.6 (CH), 127.6 (CH), 127.6 (CH), 97.3 (C), 80.7 (C), 72.6 (CH), 71.7 (C), 58.2 (CH), 57.0 (CH), 44.1 (CH), 40.7 (CH), 37.5 (CH_2), 36.8 (CH), 36.3 (CH_2), 35.9 (C), 31.1 (CH_2), 28.0 (CH_2), 27.1 ($3CH_3$), 26.8 (CH_2), 21.4 (CH_2), 19.2 (C), 17.7 (CH_3), 16.1 (CH_3), 11.5 (CH_3); HRMS-MALDI (*m*/*z*): $[M + H]^+$ calcd. for $C_{38}H_{49}NO_4Si$: 612.3503, found 612.3501.

Hemiketal 17. Under argon atmosphere, at −70 °C, to a solution of *t*-BuLi (34.0 mL, 1.6 M in pentane, 54.4 mmol) and ether (80 mL) was added 4-iodo-2-methylbut-1-ene **16** (5.40 g, 27.6 mmol) dropwise. The resulting solution was stirred at the same temperature for 30 min, and a solution of lactone **4** (8.36 g, 13.66 g) in ether (80 mL) was added. The mixture was allowed to warm to 0 °C over 3 h and quenched with a saturated aqueous solution of NH_4Cl. Brine (100 mL) was added, and the mixture was separated. The aqueous layer was extracted with ether (150 mL) and ethyl acetate (150 mL). The combined organic layers were dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified through column chromatography on silica gel (PE/EA: 5/1) to give **17** (8.93 g, 95.8%) as a white foam. The crude **17** was pure enough and could be used without purification. **Hemiketal 17**: Rf: 0.58 (hexane/ethyl acetate: 1/1); $[\alpha]_D^{29}$ + 18.8 (*c* 0.55, $CHCl_3$); IR (film): 3421, 2930, 1647, 1449, 1044, 994, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.64 (m, 4H), 7.45−7.33 (m, 6H), 4.85−4.78 (m, 1H), 4.73 (d, *J* = 4.0 Hz, 2H), 3.64−3.53 (m, 1H), 2.84 (dd, *J* = 10.2, 7.2 Hz, 1H), 1.73 (s, 3H), 1.23 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 9H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.2 (C), 145.8 (C), 135.9 (CH), 134.9 (C), 134.8 (C), 129.6 (CH), 127.6 (CH), 110.3 (CH_2), 108.3 (C), 99.8 (C), 81.6 (CH), 72.7 (CH), 71.9 (C), 58.4 (CH), 44.3 (CH), 44.2 (CH), 40.3 (CH), 37.6 (CH_2), 36.2 (CH_2), 35.8 (C), 31.9 (CH_2), 31.2 (CH_2),, 28.2 (CH_2), 27.1 ($3CH_3$), 27.0 (CH_2), 22.6 (CH), 21.8 (CH_2), 19.3 (C), 17.3 (CH_3), 14.1 (CH_3), 11.5 (CH_3); HRMS-MALDI (*m*/*z*): $[M + H]^+$ calcd. for $C_{43}H_{59}NO_4Si$: 682.4288, found 682.4278.

Oxymecuration−Reduction of 17. To a solution of **17** (10.71 g, 15.7 mmol) in degassed dichloromethane (200 mL) was added $Hg(OAc)_2$ (5.01 g, 23.5 mmol) at ambient temperature. The mixture was stirred for 3 h, and TLC showed the disappearance of **17**. To the solution was added $NaBH(OAc)_3$ (10.0 g, 31.4 mmol), and the reaction proceeded at ambient temperature for 20 h. The mixture was diluted with dichloromethane (200 mL) and filtered. The filtrate was washed with water and brine, dried over Na_2SO_4, concentrated under reduced pressure, and purified through column chromatography on silica gel (PE/EA: 6/1 to 3/1 to 1/1) to give **19** (7.05 g, 65.8%) as a white foam and **20** (2.91 g, 26.5%; Rf: 0.09 (hexane/ethyl acetate: 1/1)) as a white foam. When the reaction was carried out at the 0.5 mmol scale, compound **19** could be isolated in 75% yield. Compound **20** was not characterized and subjected to deprotection directly.

Compound 19. Rf: 0.32 (hexane/ethyl acetate: 3/1); $[\alpha]_D^{29}$ + 5.0 (*c* 0.40, $CHCl_3$); IR (film): cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70−7.64 (m, 4H), 7.45−7.33 (m, 6H), 4.77−4.64 (m, 1H), 3.64−3.53 (m, 1H), 2.76 (dd, *J* = 10.2, 7.6 Hz, 1H), 2.34 (dd, *J* = 17.0, 8.1 Hz, 1H), 1.33 (s, 3H), 1.20 (s, 3H), 1.15 (s, 3H), 1.04 (s, 9H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

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176.2 (C), 135.8 (CH), 134.7 (C), 129.5 (CH), 127.5 (CH), 116.9 (C), 100.7 (C), 82.1 (C), 81.2 (CH), 72.6 (CH), 72.3 (CH), 58.6 (CH), 58.2 (CH), 44.1 (CH), 42.9 (CH), 39.7 (CH), 37.7 (CH_2), 37.5 (CH_2), 37.2 (CH_2), 35.7 (C), 33.6 (CH_2), 31.1 (CH_2), 30.0 (CH_3), 28.4 (CH_3), 28.2 (CH_2), 27.0 ($3CH_3$), 26.9 (CH_2), 22.0 (CH_2), 19.1 (C), 16.7 (CH_3), 13.9 (CH_3), 11.4 (CH_3); HRMS-ESI (m/z): $[M + Na]^+$ calcd. for $C_{43}H_{59}NO_4Si$: 704.4105, found 704.4113.

3,26-Diol ***21***. A solution of **20** (2.91 g, 9.5 mmol) and TBAF·$3H_2O$ (5.0 g, 15.8 mmol) in THF (80 mL) was stirred at reflux for 3 h, concentrated under reduced pressure to remove THF, and ether was added (150 mL) to dissolve the remaining compounds. The solution was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification via column chromatography on silica gel (PE/EA: 3/1 to 1/1) provided **21** (1.49 g, 78%, possibly as an inseparable 10/1 mixture of C25-epimers) as a white solid. Its stereochemistry of C25 could not be identified by NOESY analysis. **Diol 21**: Rf: 0.10 (hexane/ethyl acetate: 1/1); $[\alpha]_D^{29}$ + 20.7 (*c* 0.50, $CHCl_3$); IR (film): 3369, 2929, 2857, 1776, 1450, 1038, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.83−4.71 (m, 1H), 3.67−3.55 (m, 1H), 3.51 (d, *J* = 11.4 Hz, 1H), 3.34 (d, *J* = 11.3 Hz, 2H), 3.10 (br s, 1H), 2.80 (dd, *J* = 10.1, 7.3 Hz, 1H), 2.50−2.27 (m, 2H), 1.23 (s, 3H), 1.13 (s, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6 (C), 117.4 (C), 100.1 (C), 86.1 (C), 81.6 (CH), 72.1 (C), 71.0 (CH), 68.6 (CH_2), 58.5 (CH), 58.1 (CH), 44.1 (CH), 42.1 (CH), 39.9 (CH_3), 37.6 (CH_2), 37.4 (CH_2), 37.2 (CH_2), 35.8 (C), 33.8 (CH_2), 30.9 (CH_2), 30.5 (CH_2), 28.1 (CH_2), 26.8 (CH_2), 23.8 (CH), 21.9 (CH_2), 16.8 (CH_3), 13.7 (CH_3), 11.4 (CH_3); Anal. Calcd. for $C_{27}H_{41}NO_5$: C, 70.56; H, 8.99; N, 3.05. Found: C, 70.23; H, 8.81; N, 2.89.

C3 Alcohol ***23*** *and Ketone* ***30***. A solution of **19** (6.473 g, 9.5 mmol) and TBAF·$3H_2O$ (5.0 g, 15.8 mmol) in THF (80 mL) was stirred at reflux for 3 h, concentrated under reduced pressure to remove THF, and added ether (150 mL) to dissolve the remaining compounds. Washed with water and brine, the solution was diluted with acetone (20 mL), and to the mixture was added Jones reagent at 0 °C until the color retained. The solution was stirred for 30 min, quenched by adding a saturated solution of NaOAc, and separated. The aqueous layer was extracted with ether (100 mL) and ethyl acetate (100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and purified through column chromatography on silica gel (PE/EA: 5/1 to 2/1) to afford ketone **30** (4.13 g, 98%) as a white solid. When needed, **23** could be isolated via column chromatography on silica gel (PE/EA: 4/1 to 1/1) in 95% yield as white solid.

C3 Alcohol ***23***. Rf: 0.19 (hexane/ethyl acetate: 3/2); $[\alpha]_D^{29}$ + 27.0 (*c* 1.0, $CHCl_3$); IR (film): 3265, 2967, 1453, 1360, 1012, 881, 516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.80−4.72 (m, 1H), 3.65−3.54 (m, 1H), 2.77 (dd, *J* = 10.2, 6.8 Hz, 1H), 2.46−2.37 (m, 1H), 1.32 (s, 3H), 1.21 (s, 3H), 1.14 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.2 (C), 117.0 (C), 100.8 (C), 82.3 (C), 81.3 (CH), 72.4 (C), 71.2 (CH), 58.8 (CH), 58.3 (CH), 44.3 (CH), 43.1 (CH), 39.9 (CH), 37.9 (CH_2), 37.6 (CH_2), 37.4 (CH_2), 37.3 (CH_2), 35.9 (C), 33.7 (CH_2), 31.0 (CH_2), 30.1 (CH_2), 28.5 (CH_3), 28.3 (CH_3), 27.0 (CH_2), 22.1 (CH_2), 16.8 (CH_3), 14.0 (CH_3), 11.5 (CH_3). HRMS-ESI (m/z): $[M + H]^+$ calcd. for $C_{27}H_{41}NO_4$: 444.3109; found 444.3120.

Ketone ***30***. Rf: 0.25 (hexane/ethyl acetate: 2/1); $[\alpha]_D^{29}$ + 19.0 (*c* 1.0, $CHCl_3$); IR (film): 2967, 1713, 1456, 1364, 1242, 1002, 877, 516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.81−4.69 (m, 1H), 2.83−2.73 (m, 1H), 1.32 (s, 3H), 1.23 (s, 3H), 1.14 (s, 3H), 1.04 (s, 3H), 1.03 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.7 (C), 175.7 (C), 116.9 (C), 101.0 (C), 82.4 (C), 81.2 (CH), 72.3 (C), 58.2 (CH), 58.1 (CH), 45.6 (CH), 44.2 (CH_2), 43.1 (CH), 39.7 (CH), 38.7 (CH_2), 37.8 (CH_2), 37.8 (CH_2), 37.2 (CH_2), 35.9 (C), 33.6 (CH_2), 30.1 (CH), 28.5 ($2CH_3$), 26.6 (CH_2), 22.2 (CH_2), 16.8 (CH_3), 14.0 (CH_3), 10.7 (CH_3); HRMS-ESI (m/z): $[M + H]^+$ calcd. for $C_{27}H_{39}NO_4$: 442.2952, found 442.2936.

Diketone ***25***. A solution of **23** (86.0 mg) and $Mo(CO)_6$ (26.5 mg) in MeCN/water (9 mL/1 mL) was stirred at reflux for 1 h. The solvent was evaporated under reduced pressure; the residue was purified by column chromatography on silica gel (PE/EA: 1/1) to give diketone **25** (87 mg, 99%) as a white solid. **Diketone 25**: Rf: 0.22 (hexane/ethyl acetate: 3/2); $[\alpha]_D^{29}$ + 15.3 (*c* 1.0, $CHCl_3$); IR (film): 2930, 2856, 1778, 1427, 1361, 1110, 703, 506 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.61−4.53 (m, 1H), 3.65−3.54 (m, 1H), 3.26 (dd, *J* = 11.2, 8.8 Hz, 1H), 2.45−2.35 (m, 1H), 2.13 (s, 3H), 1.27 (s, 3H), 1.10 (s, 3H), 0.85 (d, J = 6.6 Hz, 3H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.9 (C), 207.1 (C), 115.4 (C), 82.0 (C), 73.0 (CH), 71.2 (CH), 60.4 (CH), 52.7 (CH), 52.5 (CH), 44.9 (CH), 40.7 (CH), 40.3 (CH), 38.2 (CH_2), 37.7 (CH_2), 37.6 (CH_2), 37.5 (CH_2), 35.0 (C), 33.7 (CH_2), 32.0 (CH_3), 31.1 (CH_2), 31.0 (CH_2), 30.0 (CH_3), 29.6 (CH_2), 28.7 (CH_2), 28.3 (CH_3), 12.0 (CH_3), 11.3 (CH_3); HRMS-ESI (m/z): $[M + Na]^+$ calcd. for $C_{27}H_{42}O_5$: 469.2924, found 469.2915.

Ritterazine Analogue ***34***. A solution of ketone **30** (441 mg, 1.0 mmol) in ether (10 mL) was cooled to 0 °C and a precooled solution of PTAB (432 mg, 1.15 mmol) in ether (10 mL) was added rapidly via cannula. The resulting orange solution deposited copious precipitate and faded to a beige color within 2 min. After 15 min of stirring at 0 °C, the reaction was quenched with saturated aqueous $Na_2S_2O_3$ solution and brine. The mixture was extracted with ethyl acetate. The combined organic portions were dried over Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in dry DMF (5 mL) and treated with NaN_3 (195 mg, 3.0 mmol) at 0 °C for 7 h. The reaction mixture was diluted with ether ether (40 mL) and washed with water for three times, and the aqueous phase was back-extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. To the solution NaHTe in EtOH (prepared by heating powdered tellurium (382 mg, 3 mmol) and $NaBH_4$ (225 mg, 6 mmol) in degassed EtOH at 80 °C for 1 h) was added a solution of crude **31** in EtOH/ether (5 mL/4 mL). The resulting mixture was stirred at ambient temperature for 1 h under argon and for 12 h in air. The mixture was filtered through a 3 cm pad of diatomaceous earth and washed with ethyl acetate and dichloromethane. The filtrate was concentrated under reduced pressure and purified through column chromatography on silica gel (PE/EA: 1/1 to 2/3) to give **34** (132 mg, 30%) as an off-white solid.

34. Rf: 0.32 (hexane/ethyl acetate: 1/3); $[\alpha]_D^{29}$ + 69.7 (*c* 0.50, $CHCl_3$); IR (film): 2965, 1443, 1364, 1242, 1002, 877, 516 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.82−4.69 (m, 2H), 2.90−2.50 (m, 11H), 2.26 (dd, *J* = 18.4, 10.6 Hz, 2H), 1.34 (s, 6H), 1.25 (s, 6H), 1.16 (s, 6H), 1.05 (d, *J* = 6.7 Hz, 6H), 0.82 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9 (C), 148.6 (C), 148.3 (C), 117.0 (C), 101.1 (C), 82.4 (C), 81.3 (CH), 72.5 (C), 58.3 (CH), 58.2 (CH), 45.9 (CH_2), 43.2 (CH), 41.2 (CH), 39.5 (CH), 37.8 (CH_2), 37.3 (CH_2), 35.8 (CH), 34.9 (CH_2), 33.6 (CH_2), 30.2 (CH_3), 28.5 (CH_3), 28.1 (CH_2), 26.8 (CH_2), 22.1 (CH_2), 16.8 (CH_3), 14.1 (CH_3), 11.4 (CH_3); Anal. Calcd. for $C_{54}H_{74}N_4O_6$: C, 74.11; H, 8.52; N, 6.40. Found: C, 73.94; H, 8.55; N, 6.76.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02391.

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

Crystallographic data for **30** (CIF)

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