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Convergent Approach to the Tetracyclic Core of the Apparicine Class of Indole Alkaloids via a Key Intermolecular Nitrosoalkene Conjugate Addition

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Supporting Information

ABSTRACT: Readily available methyl 3-formylindol-2-ylacetate and *N*-tosyl-4-chloro-3-piperidone oxime have been used to construct the tetracyclic skeleton of the apparicine class of monoterpene indole alkaloids in only four steps in 80% overall yield. Key transformations in this convergent approach involve use of an intermolecular ester enolate/nitrosoalkene conjugate addition to form the C-15/16 bond, followed by a reductive cyclization to construct the C-ring of the tetracycle.

Monoterpenoid indole alkaloids, which are most commonly composed of a tryptamine moiety attached to a C_9- or C_{10}-terpene fragment, constitute one of the largest known classes of natural products, with over 3000 compounds having been isolated to date.[1] A small subclass of monoterpene indole alkaloids is characterized by the loss of one of the two carbons of the tryptamine unit (i.e., 5-nor-stemmadenine alkaloids).[2] The first such alkaloid to be reported is (−)-apparicine (**1**), a tetracycle isolated from *Aspidosperma dasycarpon* in 1965 (Figure 1) and subsequently found in a

1 (-)-apparicine

2 R = H, R' = Me (*E*)-vallesamine
3 R = Me, R' = H (*Z*)-vallesamine

4 (+)-16-hydroxy-16,22-dihydroapparicine

5 R = Me, R' = H ervaticine
6 R = H, R' = Me conolidine

7 (+)-alstonamine

8 (+)-angustilobine A

Figure 1. Structures of apparicine and related alkaloids.

number of other plants.[2,3] This alkaloid has been shown to have both antimicrobial and antiviral activity.[4] About 20 other monoterpenoid indole alkaloids structurally related to apparicine have subsequently been discovered. This group includes the vallesamines (**2** and **3**), which were isolated from *Vallesia dichotoma*.[5] Some more highly functionalized alkaloids having a ring skeleton similar to apparicine, exemplified by (+)-16-hydroxy-16,22-dihydroapparicine (**4**),[6] (+)-ervaticine (**5**),[7a] (+)-conolidine (**6**),[7b] (+)-alstonamine (**7**),[8] and (+)-angustilobine A (**8**),[9] have been found in various plants.

The amount of synthetic work directed toward this group of alkaloids is relatively limited. In 1977, Joule and co-workers reported the first approach to a synthesis of apparicine.[10] Their strategy involved introducing the C-6 one-carbon bridge of these alkaloids via a Mannich reaction of a 2-piperidyl indole such as **9** (Scheme 1). However, it was found that the C-16-

Scheme 1. Joule Approach to the Apparicine Skeleton

9a R' = H_2
9b R' = OCH_2CH_2O

10

11

12

13

unsubstituted system **9a** did not cyclize to **11**, although the ketal derivative **9b** did produce the desired tetracyclic apparicine model product **13** under high dilution but only in low yield. These results were attributed to conformational effects of the intermediate iminium ions. Thus, the requisite twist boat piperidine iminium ion derived from **9a**, probably for steric reasons, exists as the unreactive conformer **10**, whereas the ketal system can more easily attain the reactive conformation **12**. Moreover, it was found that introducing a hydroxyethyl substitutent group into the piperidine at C-20 in systems related to ketal **9b** completely suppressed the desired Manich cyclization.

In 2009, the Bennasar group reported the first total synthesis of apparicine (**1**) via a strategy quite different from that explored by Joule.[11] In this successful approach, the eight-membered C-ring of **1**, containing the C-6 carbon, was constructed first, followed by appending the piperidine D-

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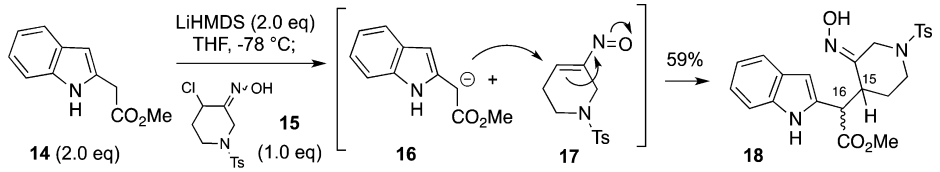
Scheme 2. Synthesis of Tricyclic Intermediate 18 via a Nitrosoalkene Conjugate Addition



ring. A year later, a formal total synthesis of apparicine was reported by Joule et al. via a new pathway which intercepted with one of the Bennasar C-ring azocane intermediates.[12]

Micalizio and co-workers have recently described a total synthesis of conolidine (**6**), a non-opioid analgesic, using a successful strategy involving C-ring formation via a Mannich reaction of a piperidino indole with formaldehyde to introduce the C-6 carbon.[13] It was suggested that in this case the cyclization is promoted by the presence of an (*E*)-C-19/20 ethylidene group in the piperidine ring which helps the intermediate iminium ion attain the requisite twist boat conformation (cf. structure **12**).

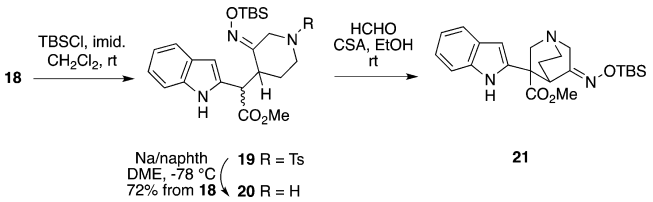
A total synthesis of (+)-16-hydroxy-16,22-dihydroapparicine (**4**) was completed by Omura and Sunazuka et al. in 2013, which led to the revision of the originally proposed structure.[14] This sequence also made use of a final-stage introduction of the C-6 carbon and C-ring via a Mannich reaction of an indole, which apparently was again promoted by the presence of an (*E*)-ethylidene group at C-19/20 in the piperidine D-ring. To date, none of the other alkaloids in this class have been targeted for synthesis.

We have been exploring the synthetic utility of both inter- and intramolecular additions of carbon nucleophiles to transiently formed nitrosoalkenes[15,16] and have recently applied this methodology as a pivotal step in total syntheses of members of the angustilodine group of monoterpene indole alkaloids.[17] We became interested in the possibility of extending the approach used for the angustilodines to develop a concise synthesis of the tetracyclic framework of the apparicine alkaloids. Thus, our synthetic plan for these alkaloids was to employ an intermolecular ester enolate/nitrosoalkene conjugate addition to form the C-15/16 bond between a piperidine and an indole moiety. We also decided to explore the construction of the C-ring via insertion of the C-6 carbon of these alkaloids by a Mannich or related process using the tricyclic product of the nitrosoalkene conjugate addition. Herein is described the results of this study.

In our first generation strategy, the idea was to make use of tricycle **18** which we have previously reported (Scheme 2).[17b] To prepare this compound, a monoanion was first formed from 2 equiv of readily available methylindole-2-acetate (**14**)[18] using 2 equiv of lithium hexamethyldisilazide, followed by addition of 1 equiv of α-chloroketoxime **15**[19] to the mixture. Under these conditions, 1 equiv of the anion **16** acts as a base to form transient nitrosoalkene **17** from oxime **15** via dehydrochlorination, which then combines with the remaining equivalent of anion, reacting as an ester enolate to generate Michael adduct **18** in 59% yield, along with recovered starting ester **14** which could be recycled. Compound **18** is an inconsequential 3:1 mixture of C-15/16 diastereomers but appears to be a single (*Z*)-oxime geometric isomer.[17]

Using intermediate **18**, we next investigated introduction of C-6 via a Mannich reaction analogous to that effected by the Micalizio[13] and Omura[14] groups. It was our hope that the large carbomethoxy group at C-16 and/or the oxime at C-20 acting as a pseudoethylidene group (albeit of different geometry than the C-19/20 ethylidene systems previously used) would help enforce a conformation similar to that shown in structure **12**, thereby facilitating closure of the alkaloid C-ring. Toward this end, oxime **18** was first silylated to afford O-TBS oxime **19**, and the tosyl protecting group was removed with sodium naphthalenide[20] to yield piperidine **20** (Scheme 3). Treatment

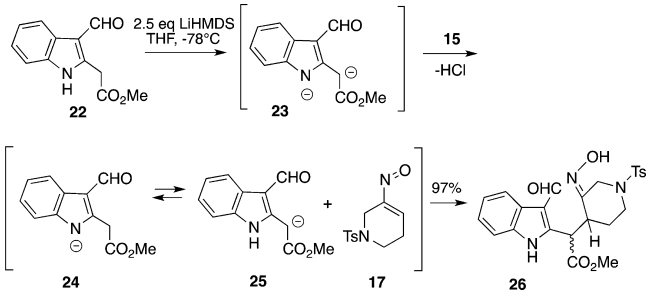
Scheme 3. Attempted Mannich Reaction of Piperidine Indole 20



of amino indole **20** with 37% aqueous formaldehyde and camphorsulfonic acid in ethanol indeed led to a Mannich product but unfortunately not the desired one. Rather, we obtained a major product to which we have tentatively assigned quinuclidine structure **21**. However, we have been unable to fully purify and characterize this compound.

In view of this result, and based on what had been learned during our work on the angustilodine alkaloids,[17] we decided to investigate a modified, potentially more efficient strategy. The plan here was to incorporate the C-6 carbon into the indole substrate prior to the nitrosoalkene/enolate condensation.[21] Thus, known 3-formylindole ester **22**[22] was treated with 2.5 equiv of lithium hexamethyldisilazide to generate dianion **23** (Scheme 4). Subsequent addition of 1 equiv of α-chloro-

Scheme 4. Ester Enolate 25/Nitrosoalkene 17 Conjugate Addition



ketoxime **15** to this dianion then led to the desired coupled product as a ~1:1 mixture of C-15/16 diastereomers **26** but as a single oxime isomer in nearly quantitative yield. As was the case with a related system in the angustilodine work,[17] we believe that this transformation proceeds via an initial dehydrochlorination of the α-chlorooxime **15** by the dianion

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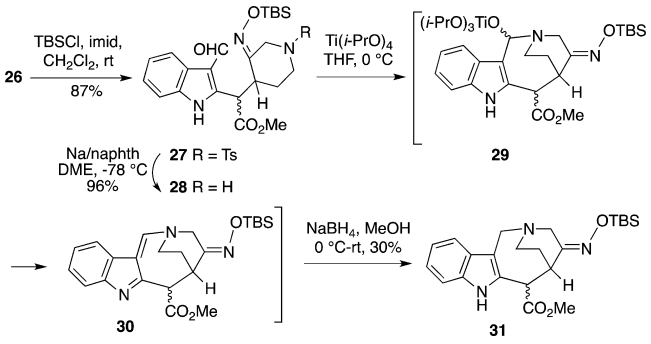
23 to generate the nitrosoalkene 17 along with a monoanion derived from the indole aldehyde ester 22. This intermediate is probably an equilibrium mixture of monoanions 24 and 25, but the conjugate addition to nitrosoalkene 17 occurs exclusively via the ester enolate form to afford product 26. This transformation is also much more efficient than that shown in Scheme 2 since no recovery/recycling of the indole moiety is required.

The diastereomeric mixture of oxime 26 was protected as the O-TBS oxime 27, and the two C-16 epimers were separated by column chromatography at this stage. Each of the pure diastereomers of 27 was then used individually for the ensuing steps to allow for full characterization (see Experimental Section and Supporting Information). The tosyl group of 27 was next removed to afford piperidine aldehyde 28 (Scheme 5).

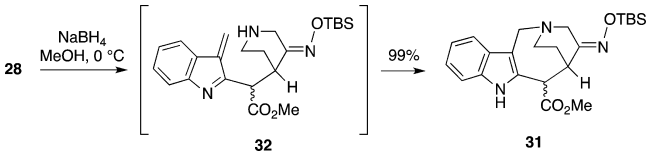
Scheme 5. Ti^{4+}-Induced Reductive Cyclization of Amino Aldehyde 28 to Tetracycle 31



Studies were then performed to effect an intramolecular reductive amination of this substrate to form the apparicine C-ring. We decided first to explore the methodology of Mattson et al., which utilizes titanium tetraisopropoxide to generate a stable tetrahedral complex like 29 from an amine and a carbonyl compound, followed by reduction, presumably via an iminium ion.[23] Thus, treatment of amino aldehyde 28 with titanium tetraisopropoxide in THF at 0 °C, followed by addition of sodium borohydride in methanol and letting the reaction mixture warm to room temperature indeed led to the desired tetracycle 31 but in only 30% yield. It seems reasonable that this transformation proceeds via elimination of 29 to form azafulvene 30 (rather than the more highly strained bridgehead iminium ion), which is then reduced by borohydride. However, since the yield for this process was not acceptable, we investigated other conditions to effect this reductive amination.

We were pleased to find that simply treating amino aldehyde 28 with sodium borohydride in methanol at 0 °C led to the apparicine tetracycle 31 in high yield (Scheme 6). This transformation probably occurs via reduction of aldehyde 28 to the corresponding alcohol, which then eliminates in situ to form the azafulvene derivative 32, followed by nucleophilic addition of the piperidine nitrogen to produce 31.[24]

Scheme 6. Direct Reductive Closure of Piperidine Aldehyde 28 to Tetracycle 31



In conclusion, we have developed a convergent and concise synthesis of the tetracyclic core of the apparicine class of alkaloids. Starting from readily available indole aldehyde ester 22 and 3-piperidone-derived α-chloroketoxime 15, it is possible to construct intermediate 31 in only four steps in 80% overall yield. Key transformations involve use of an intermolecular ester enolate/nitrosoalkene conjugate addition to form the C-15/16 bond of 31, followed by a reductive cyclization to form the C-ring of the tetracycle. We anticipate using tetracycle 31, which has handles in place at C-16 and C-20 for further elaboration, as a versatile intermediate to access a number of the apparicine alkaloids.

EXPERIMENTAL SECTION

General Methods. All non-aqueous reactions were carried out in oven- or flame-dried glassware under an argon atmosphere. All chemicals were purchased from commercial vendors and used as is unless otherwise specified. Anhydrous tetrahydrofuran and dichloromethane were obtained from a solvent purification system. Reactions were magnetically stirred and monitored by thin layer chromatography with 250 μm precoated silica gel plates. Flash column chromatography was performed using silica gel (230−400 mesh). Chemical shifts are reported relative to chloroform (δ 7.26) for ^{1}H NMR and chloroform (δ 77.2) for ^{13}C NMR. High-resolution mass spectra were obtained on a time-of-flight instrument using electrospray ionization.

Methyl 2-(3-Formyl-1*H*-indol-2-yl)-2-(3-(hydroxyimino)-1-*p*-tosylpiperidin-4-yl)acetate (26). To a solution of indole ester 22 (0.605 g, 2.78 mmol)[22] in 36 mL of THF was added 1 M LiHMDS solution in THF (6.96 mL, 6.96 mmol) at −78 °C. After 30 min, α-chloroketoxime 15 (1.050 g, 3.48 mmol)[19] dissolved in 30 mL of THF was added and the reaction mixture was stirred at −78 °C for 2 h. The reaction mixture was quenched with aqueous NH_4Cl solution and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash column chromatography (25% EtOAc/hexanes) to give a diastereomeric mixture of Michael adducts 26 (1.306 g, 97%, ∼1:1 ratio by ^{1}H NMR, yellow amorphous solid) which was carried on to the next step without separation: IR (CH_2Cl_2) 3297, 2922, 2362, 1704, 1633, 1532, 1453, 1343, 1256, 1159, 946 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.25 (s, 0.5H), 10.17 (s, 0.5H), 9.85 (s, 0.5H), 9.34 (s, 0.5H), 8.56 (br s, 1H), 8.40−8.08 (m, 1H), 7.69−7.63 (m, 2H), 7.38−7.21 (m, 5H), 5.20 (d, *J* = 6.0 Hz, 0.5H), 4.89 (d, *J* = 15.0 Hz, 0.5H), 4.79−4.71 (m, 1H), 3.66 (d, *J* = 12.0 Hz, 3H), 3.39−3.34 (m, 1H), 3.23−3.18 (m, 1H), 2.86 (br s, 1H), 2.46−2.36 (m, 3H), 1.98−1.95 (m, 1H), 1.56−1.36 (m, 1H), 1.00−0.91 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.8, 171.7, 153.0, 144.6, 141.4, 135.6, 133.3, 130.3, 128.0, 126.5, 124.3, 123.1, 119.6, 115.8, 112.4, 53.9, 53.3, 45.2, 43.2, 42.6, 42.5, 30.1, 28.3, 21.9, 1.5; HRMS-ES+ ($C_{24}H_{26}N_3O_6S$) calcd 484.1542 ($M + H^+$), found 484.1559.

Methyl 2-(3-(((*tert*-Butyldimethylsilyl)oxy)imino)-1-*p*-tosylpiperidin-4-yl)-2-(3-formyl-1*H*-indol-2-yl)acetate (27). To a solution of oxime 26 (1.346 g, 2.785 mmol) in 30 mL of dichloromethane were added TBSCl (1.260 g, 8.355 mmol) and imidazole (1.137 g, 16.700 mmol). The reaction mixture was stirred at rt for 12 h, poured into water, and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash column chromatography (25% EtOAc/hexanes) to give the separable diastereomeric silyl ethers 27 (1.452 g, 87%). The silyl ethers 27 were used separately for further steps.

Less Polar Isomer 27: Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.11 (s, 1H), 9.32 (br s, 1H), 8.24−8.21 (s, 1H), 7.61 (d, *J* = 9.0 Hz, 2H), 7.32−7.27 (m, 5H), 4.97 (d, *J* = 15.0 Hz, 1H), 4.64 (d, *J* = 9.0 Hz, 1H), 3.68 (s, 3H), 3.58−3.53 (m, 1H), 3.16−3.06 (m, 2H), 2.79−2.64 (m, 1H), 2.44 (s, 3H), 1.45−1.26 (m, 2H), 0.97 (s, 9H), 0.23 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.4, 172.2, 156.3,

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144.4, 142.4, 135.5, 133.7, 130.1, 127.9, 125.9, 124.6, 123.4, 121.1, 116.3, 111.7, 53.2, 44.9, 43.8, 42.7, 42.3, 28.1, 26.2, 21.8, 18.2, −4.8, −5.0; HRMS-ES+ ($C_{30}H_{40}N_3O_6SSi$) calcd 598.2407 (M + H^+), found 598.2399.

More Polar Isomer ***27:*** Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.27 (s, 1H), 9.61 (br s, 1H), 8.12−8.10 (m, 1H), 7.64 (d, J = 6.0 Hz, 2H), 7.42−7.25 (m, 5H), 5.24 (d, J = 6.0 Hz, 1H), 4.97 (d, J = 15.0 Hz, 1H), 3.72 (s, 3H), 3.65−3.61 (m, 1H), 3.44−3.32 (m, 2H), 3.02−2.98 (m, 1H), 2.34 (s, 3H), 2.01−1.96 (m, 1H), 1.37 (s, 1H), 0.90 (s, 9H), 0.32 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.2, 170.8, 157.6, 144.4, 141.1, 135.4, 133.9, 130.2, 127.9, 126.7, 124.8, 123.0, 119.6, 115.7, 112.0, 53.1, 45.0, 43.1, 43.0, 42.7, 28.1, 26.2, 21.8, 18.2, −4.2, −4.6; HRMS-ES+ ($C_{30}H_{40}N_3O_6SSi$) calcd 598.2407 (M + H^+), found 598.2402.

Methyl 2-(3-(((*tert*-Butyldimethylsilyl)oxy)imino)piperidin-4-yl)-2-(3-formyl-1*H*-indol-2-yl)acetate (28). To a solution of less polar Ts-protected amine **27** (0.532 g, 0.89 mmol) in 20 mL of DME was added Na/naphthalene solution (10 mL, 0.1 M in DME, 1 mmol) at −78 °C. The reaction mixture was stirred for 10 min at −78 °C. The mixture was quenched with aqueous NH_4Cl solution, extracted with EtOAc, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by flash column chromatography (50% EtOAc/hexanes to 100% EtOAc) to give the amine **28** (0.378 g, 96%). The same procedure was used for deprotection of the more polar Ts-protected amine **27** to produce the piperidine in comparable yield.

Less Polar Isomer ***28:*** Yellow foamy solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 1H), 10.05 (br s, 1H), 8.32−8.29 (m, 1H), 7.36−7.29 (m, 3H), 4.84 (d, J = 9.0 Hz, 1H), 4.52 (d, J = 15.0 Hz, 1H), 3.73 (s, 3H), 3.40−3.30 (m, 1H), 3.03 (d, J = 15.0 Hz, 1H), 2.91 (d, J = 15.0 Hz, 1H), 2.70 (t, J = 9.0 Hz, 1H), 1.54−1.45 (m, 2H), 0.99 (s, 9H), 0.25 (s, 3H), 0.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.8, 172.7, 160.7, 143.6, 135.8, 125.9, 124.8, 123.3, 121.4, 116.6, 111.7, 53.2, 45.5, 44.3, 43.5, 42.9, 32.7, 26.3, 18.3, −4.8, −5.0; HRMS-ES+ ($C_{23}H_{34}N_3O_4Si$) calcd 444.2319 (M + H^+), found 444.2303.

More Polar Isomer ***28:*** Yellow foamy solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.29 (s, 1H), 9.96 (br s, 1H), 8.16−8.15 (m, 1H), 7.41−7.39 (m, 1H), 7.31−7.29 (m, 2H), 7.16 (br s, 1H), 5.16 (d, J = 6.0 Hz, 1H), 4.47 (d, J = 15.0 Hz, 1H), 3.74 (s, 3H), 3.62−3.55 (m, 1H), 3.16 (s, 1H), 3.08 (d, J = 18.0 Hz, 1H), 2.86 (t, J = 9.0 Hz, 1H), 2.01−1.97 (m, 1H), 1.40−1.36 (m, 1H), 0.96 (s, 9H), 0.29 (s, 3H), 0.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.1, 171.0, 160.7, 142.3, 135.4, 126.7, 124.1, 122.9, 120.0, 115.9, 112.0, 53.0, 45.3, 43.8, 43.6, 43.1, 32.2, 30.1, 26.4, 26.0, 18.2, 1.4, −4.2, −4.5, −4.6; HRMS-ES+ ($C_{23}H_{34}N_3O_4Si$) calcd 444.2319 (M + H^+), found 444.2302.

Methyl 4-(((*tert*-Butyldimethylsilyl)oxy)imino)-1,3,4,5,6,7-hexahydro-2,5-ethanoazocino-[4,3-*b*]indole-6-carboxylate (31). To a solution of less polar amino aldehyde **28** (0.650 g, 1.465 mmol) in 120 mL of MeOH was slowly added $NaBH_4$ (1.110 g, 29.305 mmol) at 0 °C (a large amount of gas evolved). The reaction mixture was stirred at 0 °C for 1 h. The organic solvent was evaporated in vacuo, and the residue was dissolved in CH_2Cl_2. The organic phase was washed with water, dried over Na_2SO_4, and concentrated in vacuo to yield the tetracyclic amine **31** (0.617 g, 99%). The same procedure was used with the more polar amino aldehyde **28** to form tetracycle **31** in comparable yield.

Less Polar Isomer ***31:*** White solid; IR (CH_2Cl_2) 3345, 2953, 2858, 1725, 1455, 1317, 1275, 1253, 1161, 941 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.72 (d, J = 6.0 Hz, 1H), 7.34−7.29 (m, 1H), 7.25−7.14 (m, 2H), 4.93−4.85 (m, 2H), 4.52 (d, J = 15.0 Hz, 1H), 4.31 (d, J = 12.0 Hz, 1H), 3.68 (s, 3H), 3.29−3.20 (m, 1H), 3.00−2.90 (m, 2H), 2.68 (t, J = 12.0 Hz 1H), 1.96 (s, 1H), 1.51−1.48 (m, 1H), 1.32−1.19 (m, 1H), 0.98 (s, 9H), 0.24 (s, 3H), 0.18 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.5, 161.1, 136.1, 131.3, 127.7, 123.0, 120.5, 119.1, 115.1, 111.4, 55.6, 52.9, 45.7, 44.5, 43.0, 26.4, 18.4, −4.7, −4.9; HRMS-ES+ ($C_{23}H_{34}N_3O_3Si$) calcd 428.2369 (M + H^+), found 428.2359.

More Polar Isomer ***31:*** White solid; IR (CH_2Cl_2) 3350, 2953, 1732, 1456, 1373, 1278, 1045, 841 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (s, 1H), 7.66 (d, J = 6.0 Hz, 1H), 7.34−7.28 (m, 1H), 7.21−7.10 (m, 2H), 4.84−4.82 (m, 2H), 4.41 (d, J = 9.0 Hz, 1H), 4.29 (d, J = 15.0 Hz, 1H), 3.70 (s, 3H), 3.66−3.59 (m, 1H), 3.45−3.32 (m, 1H), 3.08−3.06 (m, 1H), 3.06−3.04 (m, 1H), 1.98−1.96 (m, 1H), 1.32−1.28 (m, 1H), 0.86 (s, 9H), 0.17−0.01 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 161.1, 135.7, 131.4, 127.4, 122.6, 120.1, 118.8, 114.7, 111.4, 55.6, 52.9, 44.1, 42.1, 30.1, 26.4, 18.2, −4.7, −4.8; HRMS-ES+ ($C_{23}H_{34}N_3O_3Si$) calcd 428.2369 (M + H^+), found 428.2364.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Proton and carbon NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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