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# Total Synthesis of (-)-Clavicipitic Acid via γ,γ-Dimethylallyltryptophan (DMAT) and Chemoselective C–H Hydroxylation

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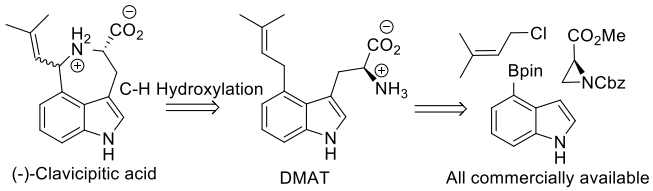



**Abstract:** The first total synthesis of natural (-)-clavicipitic acid from γ,γ-dimethylallyltryptophan (DMAT), its biosynthetic precursor, is described. This is done by a regio- and chemoselective, remote, non-directed C($sp^3$)-H hydroxylation followed by aminocyclization. This study also features a regio- and chemo-selective Pd(0)-catalyzed linear prenylation at C4 of L-tryptophan boronic pinacol ester derivate, the latter obtained by a Lewis acid-promoted aziridine amino acid ring opening with 4-boronated indole. In addition, these results support the hypothesis that oxidative cyclization between the amino acid nitrogen and the prenyl chain during clavicipitic acid biosynthesis can occur through the transient hydroxylated intermediate.

## Introduction

C–H functionalization is rapidly changing the way organic chemists approach molecule design and synthesis.[1] While early research focused on methods for the functionalization of relatively simple hydrocarbons,[2] only recently has C–H functionalization gained traction as a viable strategy for the synthesis of relatively complex targets[3] and late-stage

modification of drugs.[4] However, it is still a major challenge to differentiate the ubiquitous aliphatic C–H bonds in simple and complex substrates with high levels of chemo- and regioselectivity, as well as those of the functionalized product.[5]

The discovery of clavicipitic acid (**1**) (Figure 1) from Claviceps strain SD 58 was made in 1969 by the Floss group.[6] A few years later King *et al.* resolved the compound into two components which appeared to be a mixture of diastereomers.[7] The structures and stereochemistry of these intriguing indole-alkaloids were first elucidated with the aid of X-ray crystallography[8], but only in 2010 did Jia *et al.* establish the correct relative configurations of *cis*- and *trans*-clavicipitic acid.[9] Early studies revealed γ,γ-dimethylallyltryptophan (DMAT, **2**),[10] as the biosynthetic precursor to clavicipitic acid (as well as all other ergolines).[11] The terpenoid portion arrives from dimethylallyl pyrophosphate (DMAPP), after which formal aminocyclization forges the carbon-nitrogen bond (Figure 1a). Despite an enzyme, termed DMAT oxidase was characterized from Claviceps, nature appears to indiscriminately produce clavicipitic acid without stereocontrol.[12]

Attracted by this unique chiral tricyclic azepinoindole system and its unknown formation mechanism, numerous studies have investigated the synthesis of clavicipitic acid, both racemic and optically active. Over the years, a general strategy was developed for its total synthesis (Figure 1b).[13] Surprisingly, nobody reported the use of DMAT as an intermediate, probably because both selective direct intramolecular oxidative C–H/N–H coupling and tandem redox/cyclization combination pose significant challenges.[14] Herein, we disclose a simple 4-step route to (-)-clavicipitic acid (**1**), traversing DMAT (**2**). It features a practical synthesis of enantiopure boronate trypthophan derivatives, the strategic use of a palladium(0)-catalyzed prenylic arylation reaction coupling, and a remarkable metal-free chemoselective oxidation of aliphatic C–H bonds (Figure 1c).

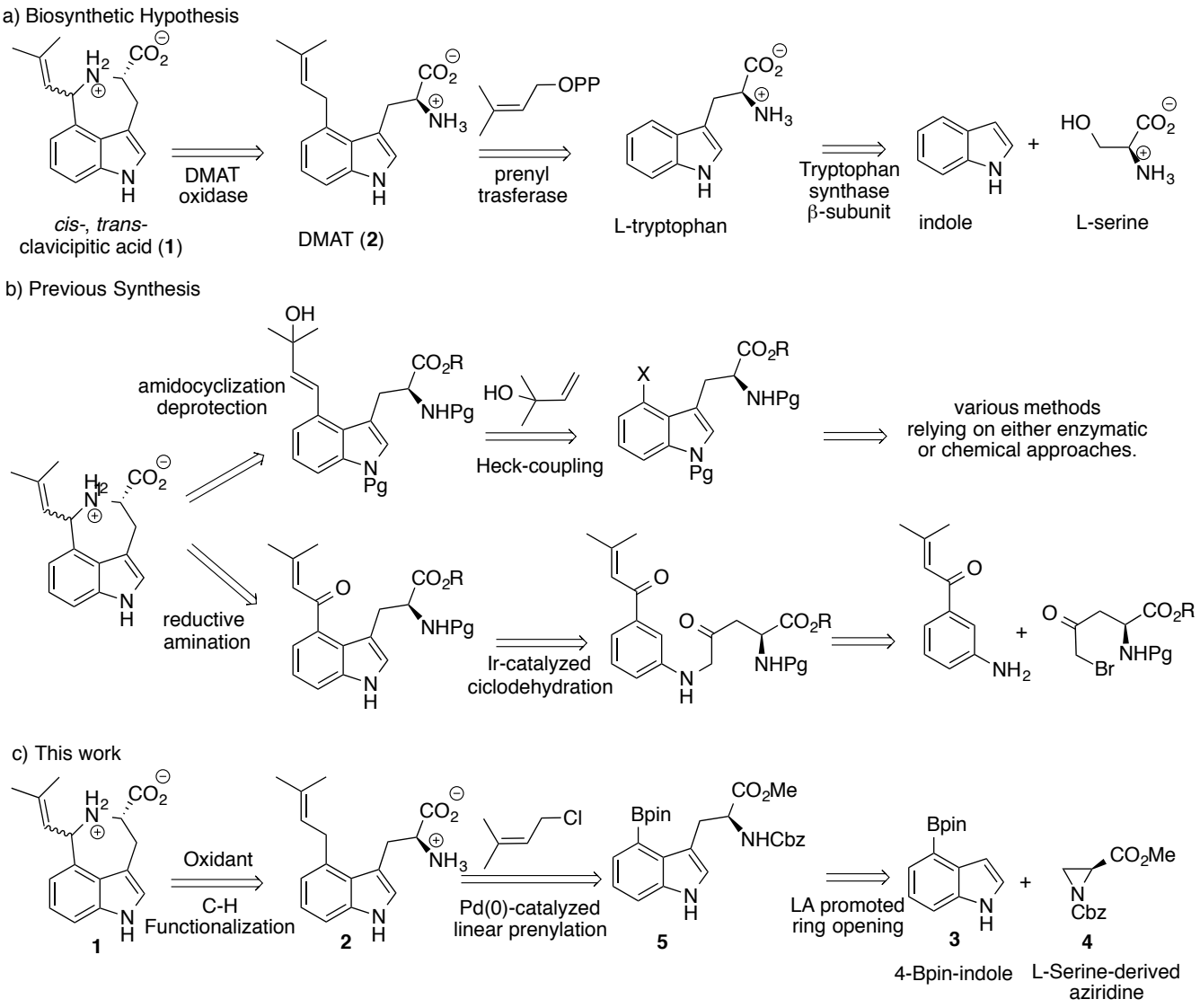



**Figure 1.** Retrosynthetic analysis for the symmetric synthesis of clavicipitic acid: a) Biosynthetic hypothesis. b) Previous synthesis. c) Envisioned C-H functionalization (our work)

Results and Discussion

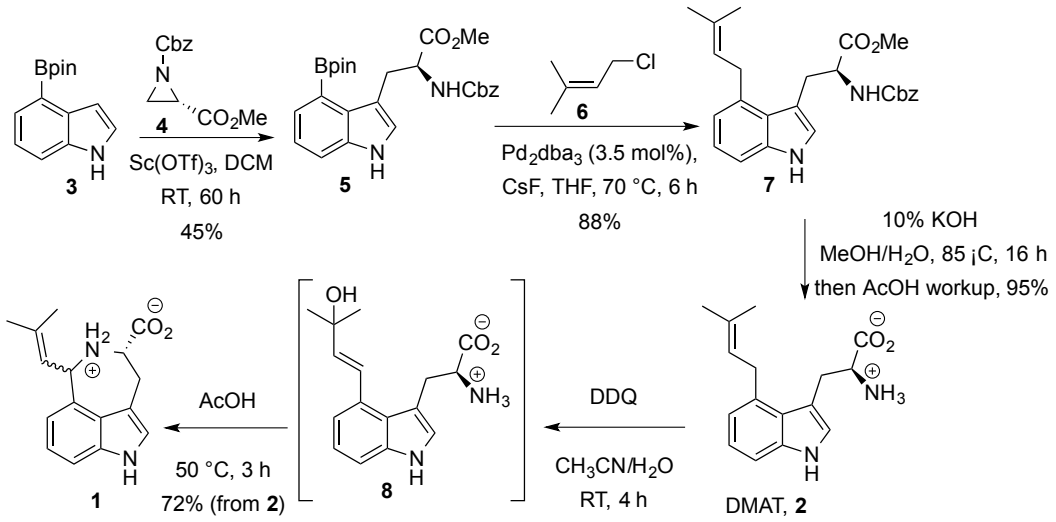
In our earlier work on the synthesis of racemic *cis*-clavicipitic acid[13d] and C4-substituted tryptophan derivatives,[15] the 4-pinacolborononate indole (**3**) has been a useful and versatile starting material. However, to affix, stereoselectivly, the amino acid side chain onto C-3 of the 4-boronate indole (**3**) in a scalable way needed heavy investigation.[16] One of the most direct routes to optically pure, noncanonical α-amino acids is the addition of a nucleophile to the least hindered β-carbon of a homochiral serine-derived aziridine.[17] Although this approach has drawbacks, such as nucleophile-dependent regioselectivity, we decided to use this fairly conventional ring-opening of enantiopure aziridine-2-carboxylates (**4**) from 4-boronate indole (**3**) in combination with an oxophilic Lewis acid.[18] Hence, inspired by the pioneering studies of Bennani,[18a]

Isobe[18b-d] and Hutton[18e] we demonstrated that L-serine-derived *N*-Cbz-aziridine methyl carboxylates opening could take place using **3** as a substrate for the preparation of enantiopure 4-boronate tryptophan derivative **5**. The treatment of both commercially available **3** and **4** in the presence of a stoichiometric amount of $Sc(OTf)_3$ in dichloromethane at room temperature afforded the protected enantiopure 4-boronate tryptophan (**5**) in 91% yield in 1:1 regioisomeric ratio (Scheme 1). Attempts to improve the regioselectivity through the use of different Lewis acid, Brønsted acid and transition metal failed or provided lower overall yields (see Table S1, Supporting Information).

The central point of our retrosynthetic strategy depends on the success of the resulting regiocontrolled union of a linear prenylated side chain fragment onto the C-4 position, followed by annulation. The palladium-catalyzed Suzuki coupling of pinacol-substituted arylboronate esters (less reactive than other aryl boron species) with allyl and related 3,3-disubstituted allyl electrophiles seemed to be well suited to this synthesis. This procedure generates the linear product in a highly regiocontrolled fashion, although it has never been tested in the context of natural product synthesis.[19] After surveying previously reported reaction conditions for the allylation of electron-rich and electron-deficient aryl pinacolboronates esters with prenylbromide, we found that $[Pd_2(dba)_3]$ with CsF, as an additive, and no added ligand in THF solvent at 70 °C provided **7** in a 2:1 mixture of linear/branched in moderate yield. Since the prenyl bromide showed good reactivity, attention was then focused on prenyl chloride, as there are no such couplings reported in the literature. The reaction produced **7** smoothly, higher-yielding (88%) which we attribute to less over-alkylation than the corresponding reactions with prenyl bromides, using prenyl chloride (1.0 equiv), $[Pd_2(dba)_3]$ (3.5 mol%), CsF (3 equiv) in THF refluxing (see Table S2, Supporting Information). Some points are noteworthy concerning this $sp^3$ carbon–aryl formation: (1) these reactions were performed in the presence of a 'ligandless' palladium catalyst (phosphine-free conditions) under conventional (thermal) reaction conditions; (2) the addition of CsF (3 equiv) reduced proto-deborylation; (3) no reaction was observed using prenyl alcohol; (4) site-selective prenylation was performed in good yield with prenyl acetate in place of prenyl chloride but mixture of linear/branched products were obtained; (5) the use of THF as a solvent emerged as preferred .[20]

To complete the synthesis of DMAT (**2**), the simultaneous removal of *N*-benzyloxycarbonyl and methyl groups was carried out using KOH in a $MeOH/H_2O$ mixture at 85 °C for 16 hours, followed by quenching with acetic acid. This step led directly to **2** by precipitation in 95% yield. Its optical purity was confirmed by comparing the specific rotation values with the reported ones: $[\alpha]^{20}_D = -45.5$ (*c* = 0.25 g/100 mL, MeOH/1N HCl 99:1) versus $[\alpha]^{20}_D = -48.5$ (*c* = 0.1 g/100 mL, MeOH/1N HCl 99:1).[10b] It is also worth to mention that, acidic hydrolysis of both methyl ester and carbamate in **7** failed, due to the abnormal reactivity of the C4-dimethylallyl side chain and/or the indolic nucleus of **7**, in strong acidic media. Pleasingly, neither alkylation nor hydrolysis caused any racemization despite the strong basic conditions. Our three-step synthesis of optically active L-DMAT (**2**) is the shortest pathway yet reported to reach this noncanonical α-amino acid.

**Scheme 1. Synthesis of (-)-DMAT and (-)-Clavicipitic Acid (1).**

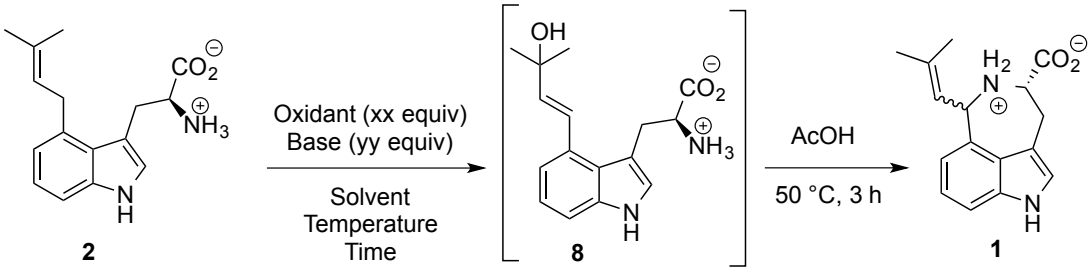



With access to **2**, we tested different reagents and conditions for the final annulation to the seven-membered azacycle. This could be either a direct oxidative cyclization (i.e., oxidative intramolecular N–H/C($sp^3$)–H coupling[21]), or more likely an indirect process where oxygenated intermediates of DMAT via C($sp^3$)–H hydroxylation undergo internal displacement to produce the clavicipitic acids.[22] Despite its apparent simplicity, this tactic faces several obstacles. Usually, it requires highly activated nitrogen sources (carbamates, sulfamates, amides, *N*-haloamides, azides, etc.) instead of free primary amines to achieve efficient nitrogen-atom transfer. Moreover, the presence of a variety of functional groups (e.g., carboxylate, amine, and alkene*)*, highly nucleophilic indole, as well as two different benzylic positions, diminishes control over regio- and chemoselectivity and hamper the use of transition-metal.[23] While a number of elegant solutions have emerged for geometrically and kinetically favored 4, 5 and 6-membered rings,[24] no examples of C–H amination to aliphatic seven-membered *N*-heterocycles are known.

Aware about oxidizing agents acting as electrophiles cannot be used and based on prior studies using **7** directly (see Tables S3 and S4 in Supporting Information) rather than a fully deprotected system **2**, we examined a metal-free C–H functionalization of **2** in $H_2O$ with acetonitrile as an organic cosolvent at room temperature. Of all inorganic or organic oxidizing agents evaluated (CAN, Oxone, PIDA, TBHP, DTBP, TEMPO, BQ and DDQ) (Table 1, entries 1-9), only DDQ generated a quantifiable amount of hydroxy substituted-DMAT **8** (Table 1, entries 10-12). In attempts to use a catalytic amount of DDQ[25] and TBN/$O_2$ as an oxidant in the reaction (Table 1, entry 13), only the starting material was recovered. Changing the cosolvent to AcOH to enhance solution acidity decreased production of **8** and led to worse overall mass recovery (Table 1, entries 14,15). Using a base ($Na_2HPO_4$) or buffer solution was detrimental for the reaction outcome (Table 1, entries 16-18). Without or with only stoichiometric water, only the starting material was observed (Table 1, entries 19-20). With only water, the conversion was very low probably due to the low solubility of **2**. The best conditions for selective

oxidation at the benzylic side chain position at C-4 turned out to be a 1:1 mixture of $CH_3CN$ and water under air, with DDQ 1.5 equiv. for 4 hours at room temperature (Table 1, entry 12).[26] No aminocylized product was observed even if more time was allowed. Since cyclization of **8**, as a potassium salt, had already been achieved[13g] by treatment with 50% aq. AcOH at 50° C for 3 h, to our pleasure we found that adding just a small amount of acetic acid allowed the complete and clean formation of seven-membered rings (**1**) in 3 hours at 50 °C (Table 1, entry 21), as a unseparable mixture (1:1) of *cis*- and *trans*- of the natural product, in 72% overall yield. Despite the fact that *cis*- is thermodynamically less stable than *trans*-clavicipitic acid,[13f] we could not observe any epimerization under these reaction conditions.

**Table 1**. Optimization of C($sp^3$)-H Hydroxylation/ Amino Cyclization of **2**



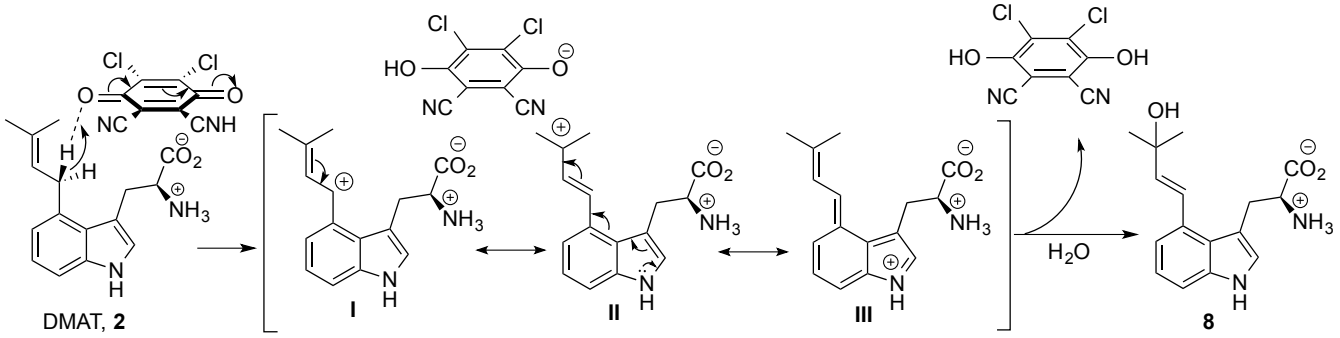

| Entry | Oxidant (equiv) | Base (equiv) | Solvent (M) | T (°C) | t (h) | Results |
|---|---|---|---|---|---|---|
| 1 | PIDA (2) | - | $CH_3CN/H_2O$ 1:2 (0.07) | RT | 1 | decomp |
| 2 | TBHP (2) | - | $CH_3CN/H_2O$ 1:2 (0.07) | RT | 16 | **2** |
| 3 | DTBP (2) | - | $CH_3CN/H_2O$ 1:2 (0.07) | RT | 16 | **2** |
| 4 | Oxone (2) | - | $CH_3CN/H_2O$ 1:2 (0.07) | RT | 1 | decomp |
| 5 | $K_2S_2O_8$ (2) | - | $CH_3CN/H_2O$ 1:2 (0.07) | RT | 1 | decomp |
| 6 | CAN (1.5) | - | DCE (0.1) | RT | 20 | **2** |
| 7 | TEMPO (2) | - | DMF (0.02) | 110 °C | 60 | **2** |
| 8 | BQ (1.5) | - | $CH_3CN/H_2O$ 1:2 (0.07) | RT | 20 | **2** and **8**: traces |
| 9 | $O_2$ (1 atm) | *t*-BuOK (3) | DMF (0.37) | RT | 16 | **2** |
| 10 | DDQ (1.2) | - | $CH_3CN/H_2O$ 1:2 (0.07) | RT | 16 | **2** and **8** |
| 11 | DDQ (1.2) | - | $CH_3CN/H_2O$ 1:9 (0.03) | RT | 2 | **2** and **8** |
| 12 | DDQ (1.5) | - | $CH_3CN/H_2O$ 1:1 (0.03) | RT | 4 | **8** |
| 13 | DDQ (0.2) | TBN (0.2), $O_2$ (1 atm) | $AcOH/H_2O$ 1/1 (0.05) | RT | 16 | **2** |
| 14 | DDQ (1.2) | - | $AcOH/H_2O$ 1/1 (0.05) | RT | 2 | CM |
| 15 | DDQ (1.2) | - | $CH_3CN/H_2O$/ AcOH 1:1:1 (0.05) | RT | 16 | CM |
| 16 | DDQ (1.2) | $Na_2HPO_4$ (10) | $CH_3CN/H_2O$ 1:2 (0.07) | 0 °C | 0.5 | CM |
| 17 | DDQ (1.2) | $NH_4OAc$ (4) | $H_2O$ (0.033) | 0 °C | 2 | CM |
| 18 | DDQ (1.2) | PBS 1M | $CH_3CN/H_2O$ 1:2 (0.03) | 0 °C | 0.5 | **2** |
| 19 | DDQ (1.2) | $MgSO_4$ (100) | $CH_3CN$ dry (0.004) | RT | 20 | **2** |
| 20 | DDQ (1.2) | $H_2O$ (2) | $CH_3CN$ (0.05) | RT | 16 | **2** |
| 21 | DDQ (1.5) | - | $CH_3CN/H_2O$ 1:1 (0.05) then AcOH | RT then 50 °C | 4, then 3 | **1**: 72%[a] |

[a]Isolated yield

The progress of the reaction between **2** and DDQ was followed by $^1$H NMR using $D_2O$ and $CD_3CN$ 1:1 mixture (see Figure S1 in Supporting Information) until the signal from the starting material disappeared ($\delta_H$ = 5.27 and 3.68 ppm) and the signal of a new compound appeared ($\delta_H$ = 7.22 and 6.19 ppm $J$ = 16.0 Hz for both). The latter corresponds, with high confidence, to the rearranged allylic tertiary alcohol (**8**) as a single stereoisomeric product.

Based on these results and previous reports on the DDQ-mediated oxidative C–H bond cleavage,[27] we propose a tentative mechanism (Scheme 2). At the beginning, DDQ coordinates with **2** to form a charge-transfer complex (appearance of strong brown color) or an electron donor–acceptor (EDA) complex. Oxidation of the substrate occurs by net, direct hydride transfer from the benzylic- dimethylallyl unit C-H bond of the C4- side chain to the carbonyl oxygen on DDQ, thereby generating **I**. Here the carbocation is stabilized by both the indole ring and the Δ2-olefin, forming an ion-pair product (negative DDQ, positive DMAT substrate).[28] Next, the resonance-stabilized carbocation intermediate (**II**) rapidly intercepts water, furnishing the oxidative C-H functionalized product **8**. The rapid intermolecular trapping of the transient carbocation by water and the related stabilization effect of the conjugated product **8** might be the thermodynamic driving force for this polarity-matched coupling. In this framework, the pendant carboxylate group species might engage in electrostatic association with the positively charged intermediate. This hypothesis is consistent with the lack of reactivity of other oxidating agents and the detrimental effect of basic and acid media on both reactivity and conversion. It is interesting to note that we never observed the alternative route, where carbocation **I** is quenched by the amine nitrogen to produce a rigidified seven-membered ring system. Rather, in many indole alkaloid pathways, the amide nitrogen originally derived from tryptophan acts as a nucleophile to attack the C2 position of the indole ring to form a 6–5–5 ring system. Collapse of the ion pair to a quinol ether product and deprotonation to a diene product were not observed.

**Scheme 2.** Plausible Pathway to Generate the Cation Intermediate, and Formation of Hydroxylated Intermediate.




Although we are not sure about the predominant factors that govern reactivity and site selectivity for C–H hydroxylation of **2** with DDQ among bond strength, conjugation, steric and stereoelectronic effects, we can assume that the amino acid substrate needs to be protonated (the amino group at least) and that the solvent mixture strongly engages in hydrogen bonding (water ideally) in order to deactivate, via polarity reversal, the adjacent C–H bonds, directing oxidation to more remote and less deactivated C–H bonds and preventing overoxidation of the product.[29]

Conclusions

In conclusion, we have reported the syntheses of both L-DMAT and L-clavicipitic acid relying on reactions and approaches that appeared only recently. Additional salient features of the route include the use of C–H functionalization logic and a maximal advantage from the bioinspired route. The combination of these strategies enables the concise synthesis of both L-DMAT (3-steps, 38% overall yield) and L-clavicipitic acid (4-steps, 27% overall yield). Remarkable in this regard is the metal-free, remote aliphatic C-H hydroxylation of L-DMAT.

## Experimental Section

**General Methods.** All reactions were run in air unless otherwise noted. Column chromatography purifications were performed in flash chromatography conditions using 230-400 Mesh silica gel or 70-230 Mesh silica gel. Analytical thin layer chromatography (TLC) was carried out on silica gel plates (Silica Gel 60 $F_{254}$) that were visualized by exposure to ultraviolet light and an aqueous solution of cerium ammonium molybdate (CAM) or *p*-anisaldehyde. $^{1}$H NMR and $^{13}$C NMR spectra were recorded on 400 spectrometer, using $CDCl_3$, DMSO-$d_6$, $CD_3OD$, $CD_3CN$, $D_2O$ and $CD_3CO_2D$ as solvent. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (*J* values) are given in hertz (Hz). In $^{13}$C NMR carbon adjacent to boron was not observed. IR spectra were obtained on FT-IR spectrometer, absorbance was reported in $cm^{-1}$. Melting points were determined on capillary melting point apparatus and are uncorrected. Optical rotation analysis was performed with a polarimeter using a sodium lamp (λ 589 nm, D-line); $[\alpha]^{D}_{20}$ values are reported in $10^{-1}$ deg $cm^2$ $g^{-1}$; concentration (c) is in g for 100 mL. HRMS analysis was performed using a Q-TOF microTM mass spectrometer.

**Starting Materials.** 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (**3**), methyl (*S*)-1-(benzyloxycarbonyl)aziridine-2-carboxylate (**4**) and 3,3-dimethylallyl chloride (**6**) are commercially available.

**Methyl (*S*)-2-(((benzyloxy)carbonyl)amino)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)propanoate (5)** To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (**3**) (3 g, 12.24 mmol) and methyl (*S*)-1-(benzyloxycarbonyl)aziridine-2-carboxylate (**4**) (3.45 g, 14.67 mmol) in DCM (34 mL) was added $Sc(OTf)_3$ (6 g, 12.24 mmol, the catalyst was added in two portions, initially and after 30 minutes). The mixture was stirred at room temperature for 24 h. The reaction was diluted with DCM (100 mL) and washed with a saturated solution of $NaHCO_3$ (1 x 150 mL) and brine (1 x 100 mL). The organic phase was dried over anhydrous sodium sulphate and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/EtOAc 7:3) to give **5** and regioisomer (5.32 g, 91%) as a mixture of regioisomers. The two regioisomers were separated by flash chromatography (gradient from DCM/$Et_2O$ = 98:2 to DCM/$Et_2O$ = 95:5) to give tryptophan derivatives **5** (2.66 g, 45%) and **regio-5** (2.42 g, 41%) as white solids. **(5):** TLC (cyclohexane/EtOAc = 7:3): $R_f$ = 0.28 (UV, CAM); TLC (DCM/$Et_2O$ = 96:4): $R_f$ = 0.34 (UV, CAM); $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 8.50 (br s, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.5, 1H), 7.26-7.25 (m, 3H), 7.20-7.16 (m, 3H), 7.09 (s, 1H), 6.74 (br s, 1H), 5.03 (d, *J* =12.5 Hz, 1H), 4.91 (d, *J* = 12.5 Hz, 1H), 4.57-4.53 (m, 1H), 3.76 (s, 3H), 3.60 (dd, *J* = 14.5, 10.5 Hz, 1H), 3.39 (dd, *J* = 14.5, 4.0 Hz, 1H), 1.41 (s, 12H); $^{13}$C{$^{1}$H} NMR (100 MHz, $CDCl_3$) δ = 173.4, 156.6, 136.6, 136.0,

130.5, 129.5, 128.3, 127.7, 127.6, 124.8, 121.0, 114.8, 112.7, 84.2, 66.4, 57.3, 52.1, 27.7, 24.9, 24.5 (carbon adjacent to boron was not observed); $^{11}$B NMR (128 MHz, $CDCl_3$): δ = 32.52; mp: 60 – 62 °C; IR (film): 3341, 1701 cm$^{-1}$; $[\alpha]^{20}_D$ = +17.4 (c = 0.41, MeOH); HRMS (ESI) m/z calcd for $C_{26}H_{32}BN_2O_6$ $(M + H)^+$ 479.2348; Found 479.2353. (**regio-5**): TLC (cyclohexane/EtOAc = 7:3): $R_f$ = 0.26 (UV, CAM); TLC (DCM/$Et_2O$ = 96:4): $R_f$ = 0.30 (UV, CAM); $^1$H NMR (400 MHz, $CDCl_3$): δ 8.49 (br s, 1H), 7.69 (d, *J* = 7.5 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 1H), 7.32 – 7.25 (m, 5H), 7.21 – 7.16 (m, 2H), 5.46 (br s, 1H), 5.17 (t, *J* = 6.5 Hz, 1H), 5.04 (s, 2H), 3.80 – 3.76 (m, 2H), 3.63 (s, 3 H), 1.39 (s, 12 H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ 174.8, 156.4, 136.7, 135.8, 129.7, 129.4, 128.4, 127.9, 123.6, 121.3, 114.7, 112.5, 83.9, 66.4, 52.0, 44.1, 42.0, 25.0, 24.7 (carbon adjacent to boron was not observed); $^{11}$B NMR (128 MHz, $CDCl_3$): δ = 30.28; mp: 54 °C; IR (film): 3339, 1708 cm$^{-1}$; HRMS (ESI) m/z calcd for $C_{26}H_{32}BN_2O_6$ $(M + H)^+$ 479.2348; Found 479.2330.

**Methyl (*S*)-2-(((benzyloxy)carbonyl)amino)-3-(4-(3-methylbut-2-en-1-yl)-1*H*-indol-3-yl)propanoate (7)** A flame-dried Schlenk tube equipped with a stir bar, under atmosphere of $N_2$, was charged with methyl (S)-2-(((benzyloxy)carbonyl)amino)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-indol-3-yl)propanoate (**5**) (1.43 g, 3 mmol), $Pd_2dba_3$ (96 mg, 0.11 mmol) and CsF (1.37 g, 9 mmol). The flask was evacuated and refilled with argon five times. THF anhydrous (63 mL) and prenyl chloride (**6**) (338 mL, 3 mmol) were added by syringe. The reaction mixture was stirred in preheating oil at 70 °C for 6 h. The mixture was diluted with EtOAc and filtered over a plug of silica gel and washed with EtOAc. The solvents were concentrated under reduce pressure and the residue obtained was purified by flash chromatography (gradient from cyclohexane/EtOAc = 8:2 to cyclohexane/EtOAc = 7:3) to give **7** (1.11 g, 88%) as white solid. TLC (cyclohexane/EtOAc = 7:3): $R_f$ = 0.28 (UV, *p*-anisaldehyde); $^1$H NMR (400 MHz, $CDCl_3$): δ 8.11 (br s, 1H), 7.34 – 7.28 (m, 5H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 2.0 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 5.33 – 5.27 (m, 2H), 5.08 (s, 2H), 4.74 – 4.78 (m, 1H), 3.80 – 3.66 (m, 5H), 3.52 (dd, *J* = 15.5, 5.5 Hz, 1H), 3.30 (dd, *J* = 15.5, 8.0 Hz, 1H), 1.75 (s, 6H); $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$): δ 172.9, 155.9, 136.9, 136.2, 134.5, 132.4, 128.5, 128.12, 128.10, 125.2, 123.7, 122.7, 122.4, 120.3, 110.6, 109.4, 67.0, 55.0, 52.3, 32.2, 29.8, 25.7, 18.0; mp: 89 – 91 °C; IR (film): 3368, 1707 cm$^{-1}$; $[\alpha]^{20}_D$ = - 40.0 (c = 0.36, MeOH); HRMS (ESI) m/z calcd for $C_{25}H_{29}N_2O_4$ $(M + H)^+$ 421.2122; Found 421.2092.

**(*S*)-2-Amino-3-(4-(3-methylbut-2-en-1-yl)-1*H*-indol-3-yl)propanoic acid (2)**

A mixture of methyl (*S*)-2-(((benzyloxy)carbonyl)amino)-3-(4-(3-methylbut-2-en-1-yl)-1*H*-indol-3-yl)propanoat (**7**) (1.26 g, 3 mmol) and 10% KOH in MeOH/ $H_2O$ 1:2 (90 mL) was stirred in preheating oil at 85 °C for 20 h. The mixture was cooled at room temperature and the MeOH was evaporated under vacuum. The solution was diluted with $H_2O$ (20 mL) and acidified with AcOH. The mixture was stirred at room temperature for 1 h and the precipitated obtained was recovered by filtration. The solid was washed with $Et_2O$, dried and then moved in a flask and coevaporated with toluene (3 x 20 mL) to give **2** (775 mg, 95%) as off white solid. TLC ($CH_3CN$/ $H_2O$ 9:1): $R_f$ = 0.12 (UV, *p*-anisaldehyde); $^1$H NMR (400 MHz, $CD_3OD$ + DCl): δ 7.25 (d, *J* = 7.5 Hz, 1H), 7.21 (s, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 5.32 – 5.29 (m, 1H), 4.16 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.80 (dd, *J* = 15.5, 3.5 Hz, 1H), 3.78 – 3.75 (m, 2H), 3.20 (dd, *J* = 15.5, 11.0 Hz, 1H), 1.78 (s, 3H), 1.75 (s, 3H); $^{13}$C{$^1$H} NMR (100 MHz, $CD_3OD$ + DCl): δ 171.6, 139.3, 134.9, 133.5, 126.0, 125.6, 125.1, 123.1, 120.9, 110.9, 108.7, 55.4, 33.2, 29.9, 25.8, 18.2; mp: 203 – 205 °C; IR (film): 3342, 1617 cm$^{-1}$; $[\alpha]^{20}_D$ = - 45.5 (c = 0.25, MeOH: 1N HCl, 99:1). Lit.[2] $[\alpha]^{20}_D$ = - 48.5 (c = 0.1, MeOH: 1N HCl, 99:1); HRMS (ESI) m/z calcd for $C_{16}H_{21}N_2O_2$ $(M + H)^+$ 273.1598; Found 273.1603. The chemical-physical data are according to the literature.[10b]

**(1*R*,3*S*)-1-(2-Methylprop-1-en-1-yl)-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole-3-carboxylic acid and (1*S*,3*S*)-1-(2-methylprop-1-en-1-yl)-2,3,4,6-tetrahydro-1*H*-azepino[5,4,3-*cd*]indole-3-carboxylic acid (1)** To a solution of (*S*)-2-amino-3-(4-(3-methylbut-2-en-1-yl)-1*H*-indol-3-yl)propanoic acid (**2**) (100 mg, 0.4 mmol) in $CH_3CN$ (4 mL) and $H_2O$ (4 mL) was added DDQ (136 mg, 0.6 mmol). The reaction mixture was stirred at room temperature for 4 h. Then AcOH (4 mL) was added and the reaction was stirred at 50 °C for 3 h. The solvents were evaporated under reduced

pressure and the residue obtained was purified by flash chromatography on 70-230 Mesh silica gel (DCM/MeOH/$NH_4OH$ 90:9:1) to give **1** as mixture (1:1) of *cis* and *trans* diastereomers (78 mg, 72%) as light yellow solid. TLC (DCM:MeOH:$NH_4OH$/75:25:3): $R_f$ = 0.18 (UV, *p*-anisaldehyde); $^1H$ NMR (400 MHz, $CD_3OD$, 1:1 mixture of *cis* and *trans* diastereomers): δ 7.34 (d, *J* = 8.0 Hz, 1H, *cis*), 7.33 (d, *J* = 8.0 Hz, 1H, *trans*), 7.22 (s, 2H, both), 7.12 (t, *J* = 8.0 Hz, 2H, both), 6.84 – 6.82 (m, 2H, both), 5.91 (d, *J* = 9.0 Hz, 1H, *trans*), 5.59 – 5.48 (m, 3H, both), 4.19 (dd, *J* = 12.5, 3.5 Hz, 1H, *trans*), 4.13 (br d, 1H, *cis*), 3.82 (dd, *J* = 16.5, 3.0 Hz, 1H, *cis*), 3.72 (dd, *J* = 16.5, 3.5 Hz, 1H, *trans*), 3.38 (dd, *J* = 16.5, 12.0 Hz, 1H, *trans*), 3.17 (dd, *J* = 16.5, 12.0 Hz, 1H, *cis*), 1.98 (s, 3H, *cis*), 1.97 (s, 3H, *cis*), 1.94 (s, 3H, *trans*), 1.88 (s, 3H, *trans*); $[\alpha]^{20}_D$ = - 68.0 (c = 0.1, EtOH). HRMS (ESI) m/z calcd for $C_{16}H_{19}N_2O_2$ $(M + H)^+$ 271.1441; Found 271.1447. The chemical-physical data are according to the literature.[13g]

**Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)propanoate (S16)** Methyl (*S*)-2-(((benzyloxy)carbonyl)amino)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)propanoate (**5**) (480 mg, 1 mmol) was placed in an autoclave with EtOAc (5 mL). Palladium 10% on graphite (100 mg, 20% in weight) and $Boc_2O$ (240 mg, 1.1 mmol) were added and the mixture was stirred under 1 atm of $H_2$ at room temperature for 2 h. The mixture was filtered through Celite and washed with EtOAc. The solution obtained was evaporated under reduced pressure to give a residue that was purified by flash chromatography (cyclohexane/EtOAc = 7:3) to give **S16** (400 mg, 90%) as white solid. TLC (cyclohexane/EtOAc = 7:3): $R_f$ = 0.25 (UV, *p*-anisaldehyde); $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.62 (br s, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.46 (d, *J* = 7.5 Hz, 1H), 7.19 – 7.16 (m, 2H), 6.44 (br d, *J* = 7.0 Hz, 1H), 4.48 – 4.46 (m, 1H), 3.75 (s, 3H), 3.62 – 3.55 (m, 1H), 3.34 – 3.30 (m, 1H), 1.45 (s, 12H), 1.28 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 173.8, 156.2, 136.0, 130.6, 129.4, 124.9, 120.9, 114.8, 113.0, 84.1, 79.2, 57.1, 52.0, 28.2, 27.8, 24.9, 24.5; $^{11}B$ NMR (128 MHz, $CDCl_3$): δ = 31.86; mp: 191 – 193 °C; IR (film): 3357, 1709 $cm^{-1}$; $[\alpha]^{20}_D$ = + 36.5 (c = 0.50, MeOH); HRMS (ESI) m/z calcd for $C_{23}H_{34}BN_2O_6$ $(M + H)^+$ 445.2504; Found 445.2520.

**Methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(4-(3-methylbut-2-en-1-yl)-1*H*-indol-3-yl)propanoate (S8)** A flame-dried Schlenk tube equipped with a stir bar, under atmosphere of $N_2$, was charged with methyl (*S*)-2-((tert-butoxycarbonyl)amino)-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indol-3-yl)propanoate (**S16**) (360 mg, 0.8 mmol), $Pd_2dba_3$ (26 mg, 0.028 mmol) and CsF (369 mg, 2.43 mmol) The flask was evacuated and refilled with argon five times. THF anhydrous (16 mL) and prenyl chloride (**6**) (91 µl, 0.81 mmol) were added by syringe. The reaction mixture was stirred in preheating oil at 70 °C for 6 h. The mixture was diluted with EtOAc and filtered over a plug of silica gel and washed with EtOAc. The solvent were concentrated under reduce pressure and the residue obtained was purified by flash chromatography (cyclohexane/EtOAc = 7:3) to give **S8** (257 mg, 83%) as white solid. TLC (cyclohexane/EtOAc = 7:3): $R_f$ = 0.31 (UV, *p*-anisaldehyde); $^1H$ NMR (400 MHz, DMSO-$d_6$): δ 10.85 (br s, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 5.30 – 5.27 (m, 1H), 4.25 – 4.19 (m, 1H), 3.67 (d, *J* = 6.5 Hz, 2H), 3.61 (s, 3H), 3.26 (dd, *J* = 15.0, 5.0 Hz, 1H), 3.07 (dd, *J* = 15.0, 9.5 Hz, 1H), 1.72 (s, 3H), 1.71 (s, 3H), 1.35 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-$d_6$): δ 173.5, 155.9, 137.3, 133.7, 131.7, 125.2, 124.55, 124.48, 121.4, 119.2, 110.5, 110.1, 78.7, 55.7, 52.2, 32.0, 29.1, 28.6, 25.9, 18.2; mp: 128 – 130 °C; IR (film): 3363, 1704 $cm^{-1}$; $[\alpha]^{20}_D$ = - 34.9 (c = 0.48, MeOH), Lit.[4] $[\alpha]^{20}_D$ = - 35.7 (c = 0.48, MeOH); HRMS (ESI) m/z calcd for $C_{22}H_{31}N_2O_4$ $(M + H)^+$ 387.2278; Found 387.2269. The chemical-physical data are according to the literature.[10a]

**(S)-2-((tert-butoxycarbonyl)amino)-3-(4-(3-methylbut-2-en-1-yl)-1H-indol-3-yl)propanoic acid (S9)** A mixture of methyl (*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(4-(3-methylbut-2-en-1-yl)-1*H*-indol-3-yl)propanoate (**S8**) (130 mg, 0.34 mmol) and 10% KOH in MeOH/dioxane 1:1.3 (3.7 mL) was stirred at room temperature for 1 h. Then the mixture was poured into $H_2O$ (10 mL) and extracted with EtOAc (3 x 5 mL). The aqueous layer was acidified with AcOH and extracted with EtOAc (3 x 8 mL). The combined organic layers were dried over anhydrous sodium sulphate and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (gradient from DCM/ MeOH 96:4 to DCM/MeOH

90:10) to give **S9** (122 mg, 97%) as a white solid. TLC (DCM/ MeOH 90:10): $R_f$ = 0.20 (UV, *p*-anisaldehyde); $^1$H NMR (400 MHz, $CD_3OD$): δ 7.18 (d, *J* = 7.5 Hz, 1H), 7.08 (s, 1H), 6.98 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 5.37 – 5.32 (m, 1H), 4.40 – 4.37 (m, 1H), 3.80 – 3.76 (m, 2H), 3.50 (dd, *J* = 15.5, 5.0 Hz, 1H), 3.16 (dd, *J* = 15.0, 9.0 Hz, 1H), 1.78 (s, 3H), 1.77 (s, 3H), 1.40 (s, 9H); $^{13}C\{^1H\}$ NMR (100 MHz, $CD_3OD$): δ 177.5, 157.9, 138.7, 135.1, 132.6, 126.5, 125.6, 124.7, 122.3, 120.3, 111.9, 110.4, 80.4, 57.1, 33.3, 30.9, 28.7, 25.9, 18.2; mp: 99 – 101 °C; IR (film): 3412, 1686 $cm^{-1}$; $[\alpha]^{20}_D$ = - 36.0 (c = 0.39, MeOH), Lit.[4] $[\alpha]^{20}_D$ = - 37.0 (c = 0.85, MeOH); HRMS (ESI) m/z calcd for $C_{21}H_{29}N_2O_4$ $(M + H)^+$ 373.2122; Found 373.2127. The chemical-physical data are according to the literature.[10a]

## Supporting Information

Analytical data ($^1$H and $^{13}$C NMR, MS) for all new compounds as well as optimization tables for **5** and **7**.

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