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# Intramolecular Aza-Diels-Alder Cyclization of a Dimerized Citral with Anilines Catalyzed by $InCl_3$

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A series of aza-polycyles containing octahydroacridine core were prepared via an intramolecular aza-Diels-Alder reaction of a dimerized citral with various aromatic amines. This reaction is efficiently catalyzed by $InCl_3$ at ambient temperature to afford the corresponding cyclized products in moderate to good yields.

**Keywords:** Aza-Diels-Alder Reaction; Indium chloride; Acridine.

## INTRODUCTION

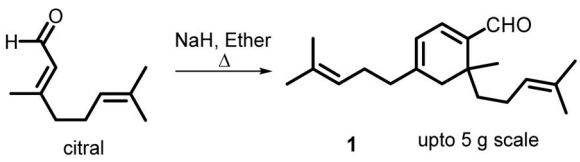
The hetero Diels-Alder reaction is a versatile tool for the construction of hetero-polycyclic systems and complex organic skeletons,[1] especially in the intramolecular versions for construction of multiple ring systems. Among various intramolecular cycloadditions, the aza-Diels-Alder reaction between *N*-arylimines and electron rich dienophile is a useful method for constructing nitrogen containing heterocycles,[2,3] such as tetrahydroquinolines,[4] octohydroacridines,[5] and others.[6]

Octahydroacridine systems are an important class of biologically active molecules and inhibitors of gastric acid secretion.[7] The use of aza-Diels-Alder method leading to this framework has been achieved with various Lewis acids such as $SnCl_4$,[8] $TiCl_3$,[9] $BiCl_3$,[10] solid supported $ZnCl_2$.[11] In addition, ionic liquids were found to efficiently accelerate the cycloaddition.[12,13]

$InCl_3$ has been known to be an efficient catalyst for a variety of transformation such as Mukaiyama aldol reaction,[14] imino Diels-Alder reaction,[15] Mannich-type reaction,[16] reductive Friedel-Craft alkylation,[17] rearrangement of epoxides,[18] preparation and reactions of allylindium reagents,[19] Diels-Alder reaction in water.[20] Apart from these remarkable applications, $InCl_3$ is a readily available, economically moderate and found to maintain its catalytic ability even in the presence of amines and water. We herein report the synthesis of functionalized octahydroacridine derivatives via an efficient intramolecular aza-Diels-Alder reaction of a dimerized citral catalyzed by $InCl_3$.

## RESULTS AND DISCUSSION

Citral is known to undergo self-condensation in the presence of proline or NaH to yield 1,2,4-trisubstituted cyclohexadienal **1** (Eqn. 1).[21] We speculated that molecules of this kind could serve as a suitable substrate in the aza Diels-Alder reaction and provide molecular complexities and structural diversities especially in a Lewis acid catalyzed one pot protocol. We prepared compound **1** in a multi-gram scale reaction under NaH promoted conditions.




(1)

To study the intrinsic aspects of **1** towards the aza Diels-Alder reaction, we conducted a reaction between equimolar amounts of **1** and aniline **2a** (R = H) in presence of a catalytic amount $InCl_3$ (20 mol%) (Scheme 1). Fortunately, the tetracyclic adduct **3a** was obtained as the only isolated product with high *trans*-selectivity in 42% yield. Dichloromethane was the best choice of the solvent as diethyl ether, tetrahydrofuran, hexanes, were found to be less efficient. Performing the reaction in dry acetonitrile gave a similar yield. Structural characterization of **3a** was established by the NMR spectroscopy. $^1H$ and $^{13}C$ NMR shifts corresponding to the octahydroacridine core were similar to those reported data.[13] Chemical shifts corresponding to the aliphatic side chain at C-3 position are essentially similar to those in **1**. Signals for the aromatic protons of **3a** are in the range of $\delta$ 6.55 ~ 7.21 with the expected splitting patterns. Both protons at C-1 and C-2 show a complicated splitting pattern, indicating a long-range H-H coupling.

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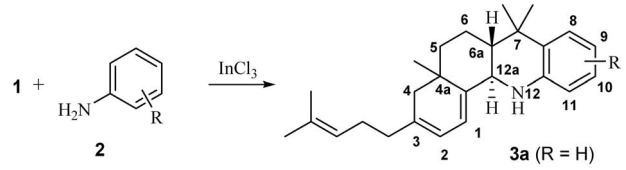
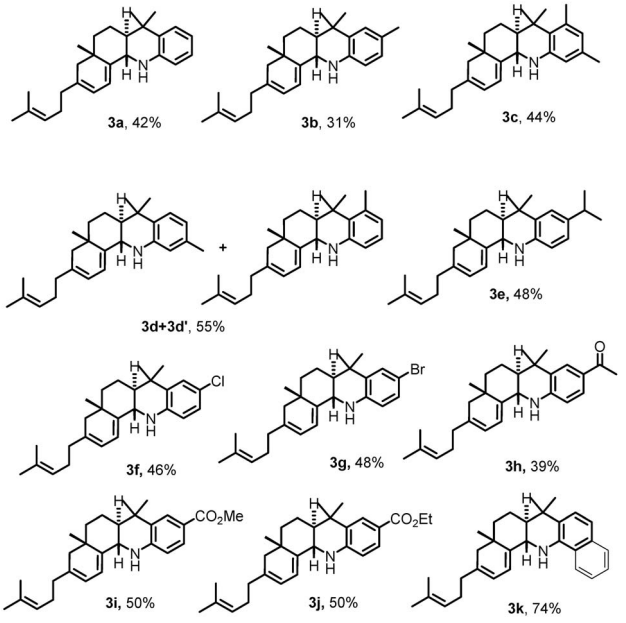
The *trans*-fusion at C-6a and C-12a was amply supported by the H-H coupling value $J$ = 10 Hz, which is similar to those reported for octahydroacridines in *trans* isomers.[13]

**Scheme 1** Aza-Diels-Alder reaction of **1** with anilines




With this result in hand, screening the scope of aryl amines with a wide range of functional groups and substituents was investigated. As shown in the Scheme 2, various anilines underwent the reaction smoothly to afford the desired products. The reaction was not hampered by methyl substituents at *para*- or the 3,5-*meta* positions (entries **3b, 3c**). For the substrate *m*-toluidine yielded a regio-isomeric mixture in a ratio of 1: 0.7, which could not be separated by column chromatography (entries **3d** and **3d'**).

**Scheme 2** Substrate scope with various aryl amines[a]

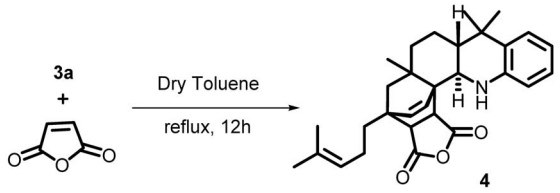



[a] isolated yields after column chromatography.

Aniline with an isopropyl group at *para*-position furnished the corresponding adduct in 48% yield accompanied with some unidentified products presumably due to the oligomerization (entry **3e**). To investigate the functional group tolerance of this strategy, a series of anilines with halogens, methoxycarbonyl, ethoxycabonyl and acetyl groups at *para*-positions (entries **3f~3j**) were examined and provided satisfactory yields. Naphthylamine was readily reacted with **1** under the similar conditions, resulting in a better yield (74%, entry **3k**) probably due to the reactivity of the additional aromatic ring.

The efficiency of this reaction was found to be influenced strongly by steric and electronic variations on the aniline substrates. The reactions with electron-withdrawing functional groups such as 3,5-bis(trifluoromethyl)aniline, 2-amino-4-chlorobenzoic acid, *p*-nitroaniline and sterically crowded 2-aminobiphenyl resulted the products in poor yields (less than 10%).

We next examined the possibility for the Diels-Alder reaction with **3**. Thus, **3a** was treated with maleic anhydride in toluene under refluxing conditions for 12h. Thermal Diels-Alder reaction proceeded smoothly in an intermolecular fashion producing the pentacyclic product **4** in 31% isolated yield, thus offering a straightforward route to generate complexity and diversity of molecules (Eqn. 2). Characterization of the isolated pentacyclic product **4** was unambiguously elucidated via NMR-spectroscopic methods. The reaction was observed to be diastereoselctive to provide the cis-isomer exclusively. The assignment of *cis* ring fusion at the newly formed ring was established by the H-H coupling constant of 8.5 Hz between them, as observed in Diels-Alder cycloadditions of similar systems.[22]




(2)

In summary, we have demonstrated a versatile protocol for the preparation of novel series of aza-polycyclic compounds by means of aza Diels-Alder cycloaddition employing dimerized citral **1** as a convenient substrate. This method describes a synthesis of octahydroacridine derivatives in high *trans*-selectivity. The use of economically affordable $InCl_3$ makes this protocol simple, convenient, and operationally practical. Further functionalization through intermolecular Diels-Alder reaction increases the complexity and may find application in natural product synthesis and drug chemistry.

## EXPERIMENTAL

**General:** All aniline derivatives were purchased from commercial sources and used without further purification. The reactions were performed under nitrogen atmosphere. Anhydrous $CH_2Cl_2$ was obtained by distillation over calcium hydride immediately before use. For chromatographic purification silica gel (70-230 μm) was used. The identification of the final compounds was confirmed by $^1$H-NMR, $^{13}$C-NMR and ESI-HRMS spectrometry. NMR experiments were recorded on a 400 MHz instrument using TMS as internal standard.

**Preparation of 6-methyl-4,6-bis(4-methyl-3-penenyl)-1,3-cyclohexadiene-1-carboxaldehyde (1):** To a solution of sodium hydride (60% in mineral oil, 700 mg, mmol) in anhydrous diethyl ether (100 mL) was added citral (5.6 mL, 32.8 mmol) slowly under nitrogen atmosphere. After being refluxed for 30 min, the reaction mixture was allowed to stir at room temperature for 2 h. The mixture was quenched with ice water and extracted with ether (2 × 30 mL). The organic extracts were washed with brine (30 mL) and dried over anhydrous $MgSO_4$ before being concentrated under reduced pressure. Further purification by flash column chromatography yielded the title compound 1 (4.0 g, 96%) as viscous oil. IR (KBr): 1670 cm$^{-1}$ ($\nu_{co}$); $^1$H NMR (400 MHz, $CDCl_3$) δ 9.34 (s, 1H), 6.59 (d, $J$ = 5.7 Hz, 1H), 5.85 (d, $J$ = 5.7 Hz, 1H), 4.96-5.03 (m, 2H), 2.26-2.31 (m, 1H), 2.22-2.12 (m, 3H), 1.93-1.97 (m, 1H), 1.70-1.85 (m, 4H), 1.61 (s, 3H), 1.58 (s, 3H), 1.54 (s, 3H), 1.46 (s, 3H), 1.27-1.33 (m, 1H), 1.12 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 17.5, 17.7, 23.8, 25.2, 25.6 (3C), 36.2, 37.7, 38.3, 41.9, 117.9, 123.2, 124.7, 131.1, 132.3, 141.4, 145.8, 150.7, 193.2. The spectral data are similar to the reported ones.[23]

**General procedure for the aza Diels-Alder adducts:** $InCl_3$ (0.2 eq.) was added to a mixture of 1 (1 eq.) and appropriate aniline (1.0 eq.) in anhydrous $CH_2Cl_2$ (5 mL). The reaction mixture was stirred at room temperature for 17-19 h. On completion as indicated by TLC, the reaction mixture was quenched with water and extracted with $CH_2Cl_2$ (3 × 5 mL). The organic layer was dried over anhydrous $MgSO_4$ before being concentrated under reduced pressure. The crude product was purified by silica gel flash column chromatography with elution of ethyl acetate: hexane (0:1 to 1:6) containing 1% triethylamine.

**trans-4a,7,7-Trimethyl-3-(4-methylpent-3-en-1-yl)-4,4a, 5,6,6a, 7,12,12a-octahydrobenzo[c]acridine (3a):** Brown oil (26.3 mg, 42%).$^1$H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, $J$ = 7.8, 1.2 Hz, 1H), 6.96 (dt, $J$ = 8, 1.2 Hz, 1H), 6.66 (td, $J$ = 8, 1.2 Hz, 1H), 6.55 (dd, $J$ = 8, 1.2 Hz, 1H), 5.76 (dd, $J$ = 5.6, 2 Hz, 1H), 5.67 (m, 1H), 5.11 (m, 1H), 4.00 (bs, 1H, -N-*H*), 3.76 (d, $J$ = 10 Hz, 1H), 2.07-2.19 (m, 5H), 1.81-1.83 (m, 1H), 1.73-1.77 (m, 1H), 1.67 (s, 3H), 1.61 (s, 3H), 1.45-1.56 (m, 4H), 1.34 (s, 3H), 1.16 (s, 3H), 0.99 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 142.8, 142.3, 136.7, 131.6, 131.0, 126.5, 126.4, 124.1, 117.5, 117.4, 114.8, 114.6, 49.8, 47.4, 44.2, 41.2, 37.1, 35.5, 35.2, 26.8, 26.7, 26.0, 25.7, 22.8, 20.8, 17.7; HRMS-ESI (TOF) for $C_{26}H_{36}N$ $[M+H]^+$: calcd $m/z$ = 362.2848, found 362.2845.

**trans-4a,7,7,9-Tetramethyl-3-(4-methylpent-3-en-1-yl)-4,4a,5, 6,6a,7,12,12a-octahydrobenzo[c]acridine (3b):** Brown oil (20 mg, 31%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.01 (s, 1H), 6.78 (d, $J$ = 8 Hz, 1H), 6.49 (d, $J$ = 8 Hz, 1H), 5.76 (d, $J$ = 6 Hz, 1H), 5.67 (m, 1H), 5.11 (m, 1H), 3.85 (bs, 1H, -N-*H*), 3.73 (d, $J$ = 9.2 Hz, 1H), 2.22 (s, 3H), 2.10-2.15 (m, 5H), 1.80-1.84 (m, 1H), 1.73-1.76 (m, 1H), 1.67 (s, 3H), 1.61 (s, 3H), 1.43-1.48 (m, 4H), 1.33 (s, 3H), 1.15 (s, 3H), 1.00 (s, 3H); $^{13}$C NMR (100 MHz,): δ 142.5, 140.4, 136.7, 131.6, 131.1, 127.2, 127.0, 126.5, 124.1, 117.5, 115.2, 114.8, 49.8, 47.6, 44.2, 41.1, 37.1, 35.5, 35.2, 27.1, 27.0, 26.0, 25.7, 22.8, 20.8, 20.7, 17.8; HRMS-ESI (TOF) for $C_{27}H_{38}N$ $[M+H]^+$: calcd $m/z$ = 376.3004, found 376.3006.

**trans-4a,7,7,8,10-Pentamethyl-3-(4-methylpent-3-en-1-yl)-4,4a, 5,6,6a,7,12,12a-octahydrobenzo[c]acridine (3c):** Orange oil (30 mg, 44%). $^1$H NMR (400 MHz, $CDCl_3$) δ 6.33 (s, 1H), 6.29 (s, 1H), 5.75 (dd, $J$ = 5.6, 2.4 Hz, 1H), 5.67 (m, 1H), 5.11 (m, 1H), 3.67 (d, $J$ = 10.4 Hz, 1H), 2.44 (s, 3H), 2.17 (s, 3H), 2.07-2.12 (m, 5H), 1.74-1.78 (m,1H), 1.72-1.73 (m, 1H), 1.67 (s, 3H), 1.62 (s, 3H), 1.53-1.56 (m, 4H), 1.45 (s, 3H), 1.27 (s, 3H), 0.97 (s, 3H); $^{13}$C NMR (100 MHz) δ 143.8, 142.4, 137.3, 136.8, 135.8, 131.6, 126.6, 124.1, 123.9, 117.5, 114.8, 114.7, 50.1, 48.7, 43.8, 40.7, 37.1, 36.3, 35.0, 26.5, 26.0, 25.7, 23.7, 23.6, 22.8, 20.5, 20.4, 17.8; HRMS-ESI (TOF) for $C_{28}H_{40}N$ $[M+H]^+$: calcd $m/z$ = 390.3161, found 390.3163.

**trans-4a,7, 7,10-Tetramethyl-3-(4-methylpent-3-en-1-yl)-4, 4a, 5,6,6a,7, 12,12a-octahydrobenzo[c]acridine (3d):** Yellow oil (35.7 mg, 55%): a regioisomeric mixture in 1:0.7 ratio). *Major isomer:*$^1$H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, $J$ = 7.8 Hz, 1H),6.49 (dd, $J$ = 7.8, 1.2 Hz, 1H), 6.40 (s, 1H), 5.74 (dd, $J$ = 5.6, 1.5 Hz, 1H), 5.66 (dd, $J$ = 5.6, 1.5 Hz, 1H), 5.10 (m, 1H), 3.96 (bs, 1H, - N-*H*), 3.75 (d, $J$ = 10.2 Hz, 1H), 2.20 (s, 3H), 2.09-2.15 (m, 5H), 1.78-1.81(m, 1H),1.71-1.75 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.40-1.55 (m, 4H), 1.32 (s, 3H), 1.13 (s, 3H), 0.97 (s, 3H); $^{13}$C NMR (100 MHz) δ 143.9, 142.7, 137.4, 131.6, 128.3, 127.9, 126.4, 124.1, 118.4, 117.5, 115.4, 114.8, 49.9, 47.6, 44.2, 41.2, 37.1, 35.3, 35.2, 29.7, 26.8, 26.0, 25.6, 22.8, 20.9, 20.8, 17.7; *Minor isomer:*$^1$H NMR (400 MHz, $CDCl_3$) δ 6.84 (t, $J$ = 7.4 Hz, 1H), 6.50 (d, $J$ = 7.4 Hz, 1H), 6.43 (d, $J$ = 7.4 Hz, 1H), 5.75 (d, $J$ = 5.7 Hz, 1H), 5.66-5.67 (m, 1H), 5.08-5.12 (m, 1H), 3.95 (bs, 1H, -N-*H*), 3.69 (d, $J$ = 10.6 Hz, 1H), 2.49 (s, 3H), 2.04-2.18 (m, 5H), 1.85-1.87 (m, 1H), 1.72-1.74 (m, 1H), 1.65 (s, 3H), 1.62 (s, 3H),

1.50-1.60 (m, 4H), 1.45 (s, 3H), 1.28 (s, 3H), 0.99 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 142.3, 141.5, 137.4, 136.8, 131.6, 127.5, 126.3, 124.1, 122.8, 117.5, 114.8, 114.3, 50.1, 48.7, 43.8, 40.7, 37.1, 36.5, 36.3, 35.0, 29.7, 26.4, 26.0, 23.5, 22.8, 20.5, 17.5; HRMS-ESI (TOF) for $C_{27}H_{38}N$ $[M+H]^+$: calcd *m/z* = 376.3004, found 376.3006.

**trans-9-Isopropyl-4a,7,7-trimethyl-3-(4-methylpent-3-en-1-yl)-4,4a,5,6,6a,7,12,12a-octahydrobenzo[c]acridine (3e):** Dark brown oil (34 mg, 48%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 1H), 6.85 (d, 1H, *J* = 8 Hz), 6.53 (d, 1H, *J* = 8 Hz), 5.77 (dd, *J* = 2, 5.6 Hz, 1H), 5.66 (m, 1H), 5.11 (m, 1H), 3.74 (d, *J* = 10 Hz, 1H), 2.79 (septet, *J* = 6.8 Hz, 1H), 2.07-2.19 (m, 5H), 1.79-1.88 (m, 1H), 1.72-1.76 (m, 1H), 1.68 (s, 3H), 1.62 (s, 3H), 1.44-1.50 (m, 4H), 1.32 (s, 3H), 1.19 (d, *J* = 6.8 Hz, 6H), 1.16 (s, 3H), 0.98 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ 142.8, 141.0, 138.1, 136.9, 131.8, 131.2, 124.8, 124.6, 124.4, 117.8, 115.3, 114.9, 50.1, 47.9, 44.4, 41.4, 41.3, 37.3, 35.9, 35.5, 33.7, 27.2 (2C), 26.3, 26.0, 24.6, 23.1, 21.1, 18.0; HRMS-ESI (TOF) for $C_{29}H_{42}N$ $[M+H]^+$: calcd *m/z* = 404.3317, found 404.3319.

**trans-9-Chloro-4a,7,7-trimethyl-3-(4-methylpent-3-en-1-yl)-4,4a, 5,6,6a,7,12,12a-octahydrobenzo[c]acridine (3f):** Yellow oil (32 mg, 46%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.47 (d, *J* = 8.4 Hz, 1H), 5.72 (dd, *J* = 5.6, 2 Hz, 1H), 5.66 (m, 1H), 5.10 (m, 1H), 4.02 (bs, 1H, -N-*H*), 3.73 (d, *J* = 10.4 Hz, 1H), 2.10-2.17 (m, 5H),1.79-1.85 (m, 1H), 1.73-1.79 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.46-1.58 (m, 4H), 1.30 (s, 3H), 1.14 (s, 3H), 0.97 (s, 3H); $^{13}$C NMR (100MHz) δ 142.0, 141.4, 136.9, 132.6, 131.6, 126.4, 126.3, 124.0, 121.8, 117.4, 115.9, 114.7, 49.9, 47.0, 44.2, 41.2, 37.1, 35.7, 35.2, 26.6, 26.5, 26.0, 25.7, 22.8, 20.8, 17.8; HRMS-ESI (TOF) for $C_{26}H_{35}NCl$ $[M+H]^+$: calcd *m/z* = 396.2458, found 396.2448.

**trans-9-Bromo-4a,7,7-trimethyl-3-(4-methylpent-3-en-1-yl)-4, 4a,5,6,6a,7,12,12a-octahydrobenzo[c]acridine (3g):** Yellow oil (36.5 mg, 48%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, *J* = 2.4 Hz, 1H), 7.03 (dd, *J* = 8, 2.4 Hz, 1H), 6.43 (d, *J* = 8 Hz, 1H), 5.72 (dd, *J* = 5.6, 2 Hz, 1H), 5.66 (m, 1H),5.10 (m, 1H), 4.04 (bs, 1H, -N-*H*), 3.73 (d, *J* = 10 Hz, 1H), 2.09-2.32 (m, 5H), 1.79-1.82 (m, 1H), 1.73-1.77 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.38-1.53 (m, 4H), 1.31 (s, 3H), 1.12 (s, 3H), 0.97 (s, 3H); $^{13}$C NMR (100 MHz) δ 141.9, 141.8, 137.0, 133.1, 131.6, 129.3, 129.1, 124.0, 117.4, 116.4, 114.7, 108.9, 49.9, 47.0, 44.2, 41.2, 37.1, 35.7, 35.2, 26.6, 26.5, 26.0, 25.7, 22.7, 20.8, 17.8; HRMS-ESI (TOF) for $C_{26}H_{35}NBr$ $[M+H]^+$: calcd *m/z* = 440.1953, found 440.1945.

**trans-4a,7,7-Trimethyl-3-(4-methylpent-3-en-1-yl)-4, 4a,5,6,6a, 7,12,12a-octahydrobenzo[c]acridin-9-yl)ethanone (3h):** Yellow oil (27.5 mg, 39%).$^1$H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, *J* = 1.6 Hz, 1H), 7.59 (dd, *J* = 8, 1.6 Hz, 1H), 6.49 (d, *J* = 8 Hz, 1H), 5.69 (m, 1H), 5.66 (m, 1H), 5.09 (m, 1H), 4.65 (bs, 1H, -N-*H*), 3.82 (d, *J* = 10.4 Hz, 1H), 2.47 (s, 3H), 2.09-2.17 (m, 5H), 1.83-1.88 (m, 1H), 1.71-1.81 (m, 1H), 1.66 (s, 3H), 1.60 (s, 3H), 1.41-1.47 (m, 4H), 1.39 (s, 3H), 1.11 (s, 3H), 0.99 (s, 3H); $^{13}$C NMR (100 MHz) δ 196.4, 147.3, 141.5, 137.2, 131.6, 129.7, 128.5, 127.1, 126.5, 124.0, 117.1, 114.3, 113.2, 50.2, 46.9, 44.3, 41.5, 37.0, 35.3, 26.0 (2C), 25.9, 25.8, 25.7, 23.0, 22.9, 20.9, 17.7; HRMS-ESI (TOF) for $C_{28}H_{38}NO$ $[M+H]^+$: calcd *m/z* = 404.2953, found 404.2959.

**trans-Methyl-4a,7,7-trimethyl-3-(4-methylpent-3-en-1-yl)-4,4a, 5,6,6a,7,12,12a-octahydrobenzo[c]acridine-9-carboxylate (3i):** Yellow oil (36.4 mg, 50%). IR (KBr): 1706 $cm^{-1}$ ($\nu_{co}$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 1.6 Hz, 1H), 7.64 (dd, *J* = 8, 1.6 Hz, 1H), 6.49 (d, *J* = 8 Hz, 1H), 5.69 (m, 1H), 5.66 (m, 1H), 5.09 (m, 1H), 4.54 (bs, 1H, -N-*H*), 3.82 (s, 3H), 3.81 (m, 1H), 2.09-2.17 (m, 5H), 1.82-1.87 (m, 1 H), 1.76-1.77 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.42-1.50 (m, 4H), 1.36 (s, 3H), 1.11 (s, 3H), 0.98 (s, 3H); $^{13}$C NMR (100 MHz) δ 167.6, 147.0, 141.6, 137.1, 131.6, 129.6, 128.8, 128.3, 124.0, 117.9, 117.2, 114.3, 113.5, 51.4, 50.1, 46.9, 44.3, 41.5, 37.0, 37.0, 35.3, 26.0, 26.0, 25.9, 25.7, 22.8, 20.9, 17.7; HRMS-ESI (TOF) for $C_{28}H_{38}NO$ $[M+H]^+$: calcd *m/z* = 420.2903, found 420.2900.

**trans-Ethyl 4a,7,7-trimethyl-3-(4-methylpent-3-en-1-yl)-4, 4a,5, 6,6a,7,12,12a-octahydrobenzo[c]acridine-9-carboxylate (3j):** Yellow oil (27.4 mg, 50%). IR (KBr): 1711 $cm^{-1}$ ($\nu_{co}$); $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 1.6 Hz, 1H), 7.65 (dd, *J* = 8, 1.6 Hz, 1H), 6.49 (d, *J* = 8 Hz, 1H), 5.70 (d, *J* = 5.6 Hz, 1H), 5.65 (m, 1H), 5.09 (m, 1H), 4.51 (s, 1H, -N-*H*), 4.29 (q, *J* = 7.2 Hz, 2H), 3.81 (d, *J* = 10.4 Hz, 1H), 2.09-2.17 (m, 5H), 1.85-1.88 (m, 1H), 1.75-1.82 (m, 1H), 1.67 (s, 3H), 1.60 (s, 3H), 1.42-1.54 (m, 4H), 1.38 (s, 3H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.12 (s, 3H), 0.99 (s, 3H); $^{13}$C NMR (100 MHz) δ 167.1, 146.9, 141.7, 137.1, 131.6, 129.7, 128.7, 128.3, 127.2, 124.0, 117.2, 114.4, 113.5, 60.1, 50.1, 47.0, 44.3, 41.5, 37.0, 37.0, 35.3, 26.1, 26.0, 25.9, 25.7, 22.9, 20.9, 17.7, 14.5; HRMS-ESI (TOF) for $C_{29}H_{40}NO_2$ $[M+H]^+$: calcd *m/z* = 434.3059, found 434.3062.

**trans-4a,7,7-Trimethyl-3-(4-methylpent-3-en-1-yl)-4,4a, 5,6,6a, 7,14,14a-octahydrodibenzo[c,h]acridine (3k):** Brown oil (53.2 mg, 74%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 8 Hz, 1H), 7.73 (d, *J* = 8 Hz, 1H), 7.36-7.44 (m, 1H), 7.36-7.44 (m, 1H), 7.36-7.44 (m, 1H), 7.23 (d, *J* = 8 Hz, 1H), 6.10 (dd, *J* = 5.6, 1.6 Hz, 1H), 5.77 (m, 1H), 5.15 (m, 1H), 4.45 (bs,1H, -N-*H*), 3.87 (d, *J* = 9.6 Hz, 1H), 2.14-2.26 (m, 5H), 1.86-1.88 (m, 1H), 1.70 (s, 3H), 1.64 (s, 3H), 1.48-1.61 (m, 4H), 1.41 (s, 3H), 1.25 (s, 3H), 1.05 (s, 3H); $^{13}$C NMR (100MHz) δ 142.6, 137.0, 136.8, 132.6,

131.6, 128.2, 125.6, 125.2, 125.1, 124.9, 124.1, 124.0, 120.1, 117.8, 117.6, 115.3, 49.8, 47.6, 44.3, 41.1, 37.1, 35.8, 35.4, 27.3, 26.7, 26.0, 25.7, 22.7, 20.8, 17.8; HRMS-ESI (TOF) for $C_{30}H_{38}N$ $[M+H]^+$: calcd *m/z* = 412.3004, found 412.3003.

**trans-5a,8,8-Trimethyl-4-(4-methylpent-3-en-1-yl)-3a, 4,5,5a,6, 7,7a,8, 13,13a-decahydro-4,13b-ethenoisobenzofuro [5,4-c]acri-dine-1,3-dione (4):** A mixture of **3a** (42 mg, 0.121 mmol) and maleic anhydride (15 mg, 0.157 mmol) in anhydrous toluene (2 mL) was heated under refluxing for 12h. Solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography to give **4** as a sponge material (17 mg, 31%). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 7.8 Hz, 1H), 6.90 (dt, *J* = 7.8, 1.4 Hz, 1H), 6.55 (dt, *J* = 8.2, 1.4 Hz, 1H), 6.51 (d, *J* = 8.2 Hz, 2H), 6.25 (bs, 1H), 5.90 (d, *J* = 8.2, 1H), 5.10 (t, *J* = 7 Hz, 1H), 3.76 (d, *J* = 10.2 Hz, 1H), 3.48 (d, *J* = 8.5 Hz, 1H), 3.07 (d, *J* = 8.5 Hz, 1H), 2.09-2.19 (m, 1H), 1.90-1.98 (m, 1H), 1.77-1.83 (m, 2H), 1.64 (s, 3H, Me), 1.60-1.61 (m, 3H), 1.58 (s, 3H, Me), 1.35-1.38 (m, 2H), 1.29-1.32 (m, 2H), 1.27 (s, 3H), 1.12 (s, 3H), 1.11 (s, 3H); $^{13}$C NMR (400 MHz, $CDCl_3$) δ 175.7, 169.6, 143.9, 133.8 (2C), 132.2, 129.9, 126.7, 125.6, 123.7, 116.76, 114.86, 51.9, 51.3, 49.6, 49.0, 48.1, 44.7, 40.7, 40.5, 37.7, 35.4, 35.0, 26.9, 26.6, 25.7, 25.2, 22.7, 19.9, 17.7; HRMS-ESI (TOF) for $C_{30}H_{38}NO_3$ $[M+H]^+$: calcd *m/z* = 460.2852, found 460.2846.

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