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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c01301 • Publication Date (Web): 24 Aug 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis of illudinine from dimedone and identification of activity as a monoamine oxidase inhibitor (MAOI)

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ABSTRACT: The fungal metabolite illudinine is prepared in seven steps and ca. 55% overall yield from dimedone using an "open and shut" (ring-opening and ring-closing) strategy. Tandem ring-opening fragmentation and olefination of dimedone establishes alkyne and vinyl-arene functionality linked by a neopentylene tether. Oxidative cycloisomerization then provides the illudinine framework. The key innovation in this second-generation synthesis of illudinine is the use of the nitrile functional group, rather than an ester, as the functional precursor to the carboxylic acid of illudinine. The small, linear nitrile (C≡N) is associated with improved selectivity, π-conjugation, and reactivity at multiple points in the synthetic sequence relative to the carboxylic acid ester. Preliminary assays indicate that illudinine and several related synthetic analogues are monoamine oxidase inhibitors (MAOIs), which is the first reported indication of biological activity associated with this natural product. Illudinine was found to inhibit monoamine oxidase B (MAO-B) with an IC_{50} of 18 ± 7.1 μM in preliminary assays.

INTRODUCTION

Illudinine is the alkaloid congener of illudalic acid, with both being natural sesquiterpene metabolites of the toxic jack o'lantern mushroom (*Omphalotus illudens*; aka *Clitocybe illudens*).[1] After initially being identified as "the inactive acidic compound", illudalic acid later emerged from high-throughput screening as "the first potent, selective" inhibitor of the human leukocyte common antigen-related (LAR) receptor-type protein tyrosine phosphatase (PTP),[2] which has implications for drug discovery related to insulin resistance, diabetes, obesity, CNS injury, drug addiction, and various cancers.[3] No biological activity has been identified previously for illudinine.

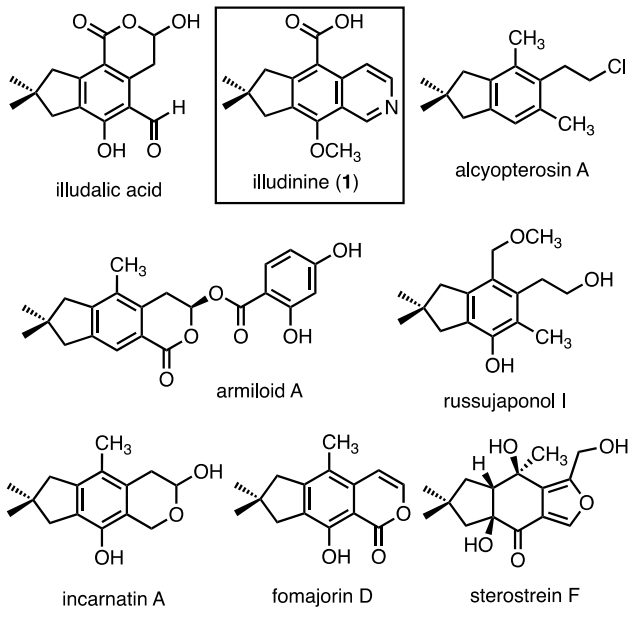
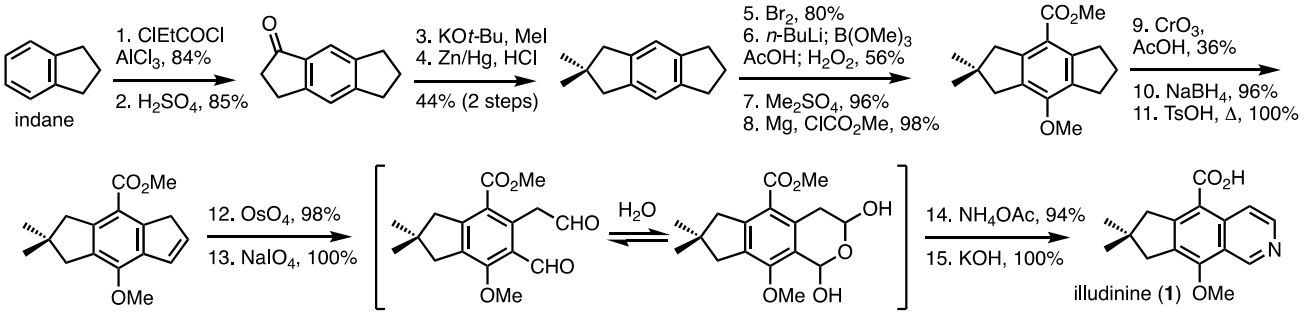


Figure 1. Selected illudalane sesquiterpenes.

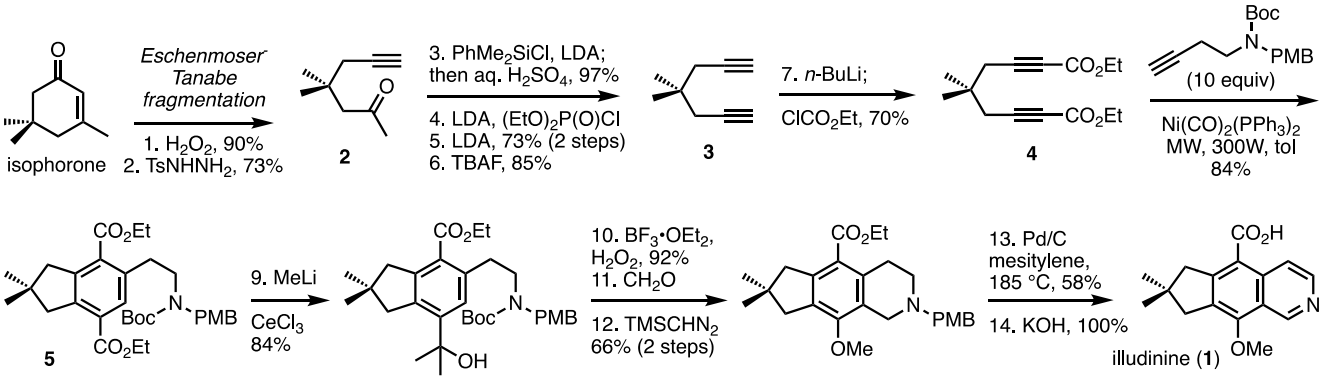
Illudalic acid and illudinine (Figure 1) are members of the illudalane sesquiterpene family of natural products. Other illudalanes include the alcyopterosins[4] and other pterosins,[5] armiloid A,[6] echinolactones,[7] fomajorin D,[8] granulolactone[9] and dihydrogranuloinden,[10] incarnatins and incarnalactones,[11] onitin,[12] russujaponols,[13] sterostreins,[14] and several unnamed illudalanes.[15] The illudalanes are biosynthetically related to the illudins and illudanes, and some illudalanes may be artifacts of the illudin/illudane isolation process.[16] The illudalanes have a variety of known biological activities, but their pharmacological development has suffered from limited access to synthetic derivatives. For example, medicinal chemistry efforts associated with the cytotoxicity of the alcyopterosins and the phosphatase inhibition activity of illudalic acid have focused on simplified synthetic analogues in which the fused *gem*-dimethylcyclopentane region has been truncated,[17] removed,[18] and/or replaced[19] with something more synthetically accessible. In all cases, these synthetically expedient structural modifications resulted in loss of potency. Improved synthetic access to the illudalanes themselves and to analogues that incorporate the desirable features of the fused *gem*-dimethylcyclopentane region are needed to advance drug discovery.

The deceptively simple illudalane carbon skeleton presents challenges for modern synthetic methodology and strategies for chemical synthesis. The bicyclo[4.3.0]nonane carbocyclic core includes a quaternary center and is often embodied as a 2,2-dimethyl-indane with full substitution around the aromatic ring (cf. Figure 1). The various illudalane sesquiterpenes have been popular targets for target-oriented synthesis, especially in recent years;[20] discussion here focuses on illudinine.

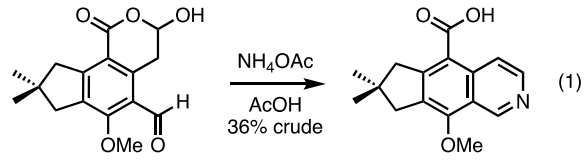
Scheme 1. Woodward and Hoye synthesis of illudinine (15 steps, 4.6% overall from indane).



Scheme 2. Teske and Deiters synthesis of illudinine (8 steps, 17% overall from diyne 3; 14 steps, 6.9% from isophorone).



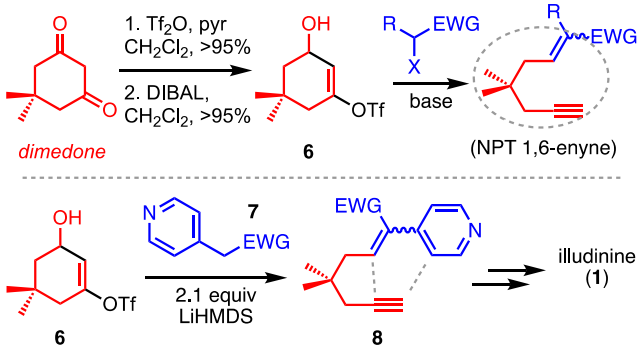
The first synthesis of illudinine (**1**) (along with illudalic acid) was published in 1977 by Woodward and Hoye in a 15-step route from indane (4.6% overall yield, Scheme 1).[21] This work highlights the close structural relationship between illudinine and illudalic acid, including the demonstration that illudinine can arise from condensation of the methyl ether of illudalic acid with ammonia (eq 1).



In 2008, Teske and Deiters developed an elegant nickel-catalyzed cyclotrimerization method (cf. **4**→**5**) that enabled an 8-step synthesis of illudinine from diyne **3** (17% overall yield, Scheme 2),[22] which itself is made from isophorone.[23] These previous syntheses of illudinine underscore the challenges associated with crafting the fused *gem*-dimethylcyclopentane ring. The Woodward approach was to anneal a dimethylcyclopentanone through a series of substitution reactions, followed by deoxygenation. Deiters made use of 4,4-dimethyl-1,6-heptadiyne (**3**), which is an attractive building block for the synthesis of many illudalanes except that it is typically prepared in 6 steps from isophorone,[23] starting with Eschenmoser–Tanabe fragmentation (→**2**).[24]

We have been developing anionic fragmentation[25] processes for making alkynes,[26] including in tandem with olefination for preparing tethered enynes.[27] This methodology provides access to neopentylene-tethered (NPT) 1,6-enynes in three steps from dimedone (Scheme 3, top). Like 1,6-diyne **3** (Scheme 2), NPT enynes are attractive building blocks for chemical synthesis. We have shown how NPT enynes derived from dimedone can advance synthetic methodology,[28] streamline previous syntheses of hirsutene and illudol,[27] support concise syntheses of alcyopterosin A[20a] and illudinine,[29] and facilitate production of synthetic illudalic acid and analogues.[20j] Our approach to illudinine begins with tandem fragmentation and Knoevenagel-type condensation of **6** with **7** to prepare pyridyl-enynes **8**, then cycloisomerization to access isoquinoline systems *en route* to the natural product (Scheme 3, bottom).

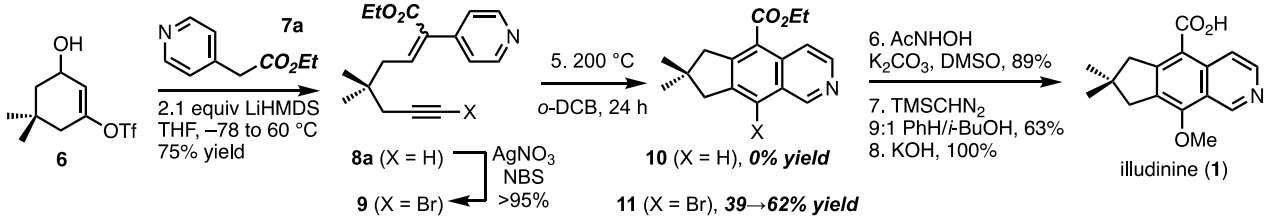
Scheme 3. Tandem fragmentation / olefination methodology and application to the synthetic approach to illudinine.



Here we report our synthesis of illudinine from dimedone, building on preliminary communications and with a key tactical innovation compared to our first-generation approach. We recapitulate the first iteration of this approach (Scheme 3, bottom, EWG = CO_2Et), updating it to include a recent focused examination of the microwave-mediated oxidative cycloisomerization.[30] For the revised approach, we used a nitrile (C≡N) functional group instead of an ethyl ester as the precursor to the carboxylic acid of illudinine (EWG = CN). The nitrile requires harsher conditions for late-stage hydrolysis to the

carboxylic acid, but illudinine itself is robust to hydrolysis.[31]

Scheme 4. First-generation synthesis of illudinine (8 steps, 14-22% yield from dimedone).



The nitrile is also smaller and more electron-withdrawing than the ester, including by virtue of better π-conjugation owing to its limited conformational freedom. These attributes of the nitrile translated into several improvements in reaction outcomes, resulting in an overall synthetic production process that is shorter (7 steps vs. 8 steps) and affords a higher overall yield (58% vs. 14-22%) from dimedone. We also report biological activity of illudinine for the first time; it is a monoamine oxidase inhibitor (MAOI), with an IC_{50} of ~18 μM for monoamine oxidase B (MAO-B) (*vide infra*).

RESULTS AND DISCUSSION

First-generation synthesis.[29,30] The synthesis of illudinine as previously reported is outlined in Scheme 4. The hydroxy-cycloalkenyl triflate (**6**) needed for fragmentation / olefination can be reached in two steps from dimedone (cf. Scheme 3, top). Tandem fragmentation / olefination is mediated by two equivalents of strong base to deprotonate the two substrates at low temperature. As the reaction mixture warms, the triflate undergoes anionic fragmentation to 3,3-dimethyl-5-hexynal (not shown), which undergoes Knoevenagel-type condensation *in situ* with pyridine **7a**. Vinyl pyridine **8a** is obtained as a ca. 2:1 mixture of *Z*:*E* isomers. From here, an oxidative cycloisomerization involving an inverse-demand dehydro-Diels–Alder reaction was envisioned based on recent precedent from the Brummond lab in the "normal" electron-demand series,[32] but inverse-demand Diels–Alder processes can be complicated by competing reaction pathways.[33] In this case, heating **8a** at temperatures up to 240 °C resulted in thermal decomposition with no evidence of the desired product (**10**, X = H). However, bromo-alkyne **9** proved to be a competent substrate, providing modest to good yields of bromo-isoquinoline **11**. Bromo-alkyne dienophiles are known,[34] and computational data suggests that the bromine substituent weakens the alkyne π-bond,[35] which thus facilitates the cycloaddition process.

Nonetheless, this oxidative cycloisomerization has a narrow reactivity window, with product formation and decomposition competing at the reaction temperatures required for reactivity. In our preliminary investigations, we examined microwave (MW) and conventional (CONV) heating methods interchangeably, and we found that MW heating for 12 h at 200 °C provided a viable 40% yield of the isoquinoline. A similar yield could be obtained by CONV heating for 24 h, but the isolated yields declined thereafter linked to product decomposition.

We later reexamined this reaction systematically, focusing on temperature, time, and heating mode (MW v CONV).[30] Yields were consistently highest at 200 °C and 24 h compared with temperatures and times above and below these values. It was also found that solutions of the substrate heat more efficiently in the microwave than solutions of the product (faster and to higher temperature at constant MW power), and that isolated yields of product were consistently higher under MW compared to CONV heating, despite essentially identical temperature profiles and other reaction variables. For example, MW heating at 200 °C for 24 h produced bromo-isoquinoline **11** in 62% yield, compared with 39% under CONV heating. Possible interpretations and strategic applications of this observed phenomena are discussed elsewhere.[36]

Replacement of the bromide with methoxide to provide illudinine ethyl ester was challenging, as discussed in our preliminary report. Direct substitution was unsuccessful in our hands, but the Maloney–Fier conditions[37] introduced a hydroxy substituent (**11**→X=OH) in 89% yield. Methylation of this hydroxy-isoquinoline (like other hydroxy-isoquinolines[38]) was highly selective for (undesired) *N*-methylation under most conditions, but a protocol involving TMS-diazomethane[38a] was carefully optimized to reverse selectivity to 70:30 favoring *O*-methylation and produced illudinine ethyl ester in 63% isolated yield. Saponification as previously reported provided illudinine in essentially quantitative yield.[29]

Our synthetic approach to illudinine had thus been reduced to practice as an 8-step synthesis in ca. 22% overall yield from dimedone (Scheme 4). These metrics compare favorably to previous syntheses (Scheme 1 and 2), but issues of selectivity and yield remained to be addressed, in particular with the thermal oxidative cycloisomerization and subsequent bromide-to-methoxide conversion.

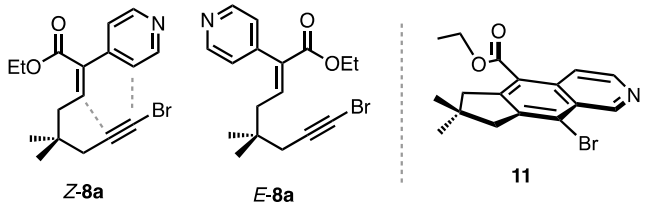
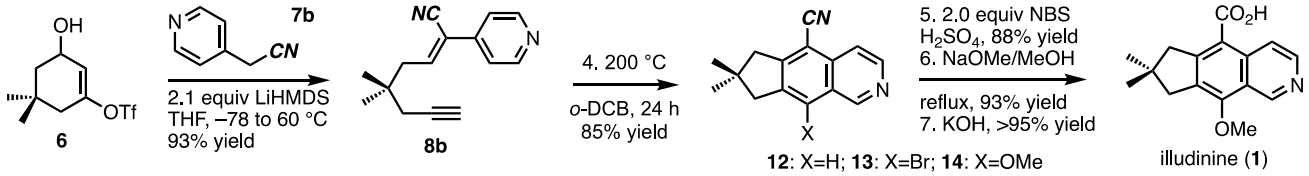


Figure 2. *left*: the *Z*- and *E*-isomers of **8a**; *Z*-**8a** is aligned for intramolecular Diels–Alder cycloaddition. *right*: perspective depiction of a conformation of bromo-isoquinoline **11** in which the ester is aligned perpendicular to the isoquinoline plane.

Considerations for process improvement. One concern we aimed to address was the 2:1 mixture of *Z*:*E* enyne isomers **8a** generated in the tandem fragmentation / olefination, which preceded the oxidative cycloisomerization. The *Z*-isomer of **8a** is appropriately disposed for intramolecular cycloaddition, whereas the *E*-isomer is not (Figure 2, left). Recovered **8a** from incomplete cycloisomerization reactions retained the ca. 2:1 ratio, suggesting that this (thermodynamic) ratio is maintained during the high temperature reaction by *in situ* *Z*/*E* isomerization, in which case the starting *Z*:*E* ratio may be moot. However, a careful chromatographic separation of **8a** provided fractions that were enriched in the *Z*-isomer, and this *Z*-enriched

Scheme 5. Second-generation synthesis of illudinine (5 steps, ca. 60% yield from 6; 7 steps, ca. 55% yield from dimedone)



material qualitatively outperformed the *Z*-depleted material in small-scale cycloisomerization reactions (not shown). This preliminary observation suggested that increasing the *Z*:*E* ratio might improve the oxidative cycloisomerization process, as would be expected if *Z*/*E* isomerization were not occurring (or were inefficient) during the high-temperature reactions.

Other concerns relate to the hypothetical conformational preferences of the ester (Figure 2, right). The ester of **11** is likely not well conjugated with the isoquinoline aromatic ring system, and we reasoned that there is similarly poor orbital overlap in rate-determining transition state structures associated with the cycloisomerization and bromide substitution processes.

With these concerns and considerations in mind, we focused on the small, linear nitrile as the functional precursor to the illudinine carboxylic acid. We formulated two hypotheses and identified two new concerns related to replacing the ester with a nitrile. The first hypothesis was that the tandem fragmentation / olefination would be more *Z*-selective with the smaller nitrile. The second was that the desired Br→OMe S_NAr substitution (cf. **13**→**14**, Scheme 5) would be better facilitated by the nitrile than the ester, owing to better π-conjugation with the aromatic ring. The two concerns were that the nitrile would be more resistant to hydrolysis in the last step than the ester, and the hypothetical impact of better π-conjugation of the nitrile in the inverse-demand Diels–Alder transition state was not assumed to be favorable to the reaction, given the general difficulties with inverse-demand Diels–Alder reactions cited above.[33] Data and observations from subsequent experimental work support the two hypotheses and suggest that the concerns were largely unfounded.

Second-generation synthesis. The revised and refined synthesis of illudinine featuring the nitrile in place of the ester is outlined in Scheme 5. As noted earlier, hydroxy-cycloalkenyl triflate **6** is available in two steps, each >95% yield, from dimedone (Scheme 3, top). 4-Pyridinylacetonitrile (**7b**) is commercially available as the HCl salt, which was convenient to use as received with an extra equivalent (3.1 equiv) of base in the tandem fragmentation / olefination step. Enyne **8b** was obtained in 93% yield as a single observable isomer, which we attribute to the small steric profile of the (two-atom) nitrile.

Pyridyl-enyne **8b** is an excellent substrate for the oxidative cycloisomerization reaction. Whereas ester variant **8a** was not a viable substrate (0% yield of **10**), nitrile **8b** was converted into isoquinoline **12** in 85% yield upon heating at 200 °C. In this case, MW and CONV heating gave similar results, and even heating neat (solvent-free) delivered **12** with similar efficiency. This positive outcome is attributed to: i) the isomeric purity of **8b**; ii) better access to planar vinylpyridine conformations that are optimal for cycloaddition; and iii) strong π-conjugation between the electron-deficient diene component and the sp-hybridized (linear) nitrile. Some of the challenges of inverse-demand Diels–Alder reactions are associated with instability of electron-deficient dienes; as noted in our preliminary report,[29] these concerns are off-set by the extra stability of vinylarene-based 4π components.

Having observed favorable reactivity from enyne **8b**, we elected to explore bromination of isoquinoline **12**, rather than return to the original plan of brominating alkyne **8b**. The *para*-cyano group was now viewed as a liability in the electrophilic aromatic bromination, but *N*-bromo-succinimide (NBS) in sulfuric acid[39] at 0 °C introduced the desired bromine atom (→**13**) in 88% yield without impacting the nitrile. In contrast to our efforts in the first-generation synthesis, sodium methoxide in refluxing methanol smoothly promoted the desired S_NAr substitution to methoxy-isoquinoline **14**. Finally, potassium hydroxide in ethanol, now under refluxing conditions, hydrolyzed the nitrile and delivered illudinine in essentially quantitative yield. As noted previously, this second-generation manifestation of our approach based on tandem fragmentation / olefination and oxidative cycloisomerization provides illudinine in 7 steps and ca. 55% overall yield from dimedone.

Monoamine oxidase B (MAO-B) bioassay data. We were interested in exploring potential biological activity of illudinine. Its congeneric natural product illudalic acid is an inhibitor of LAR phosphatase,[2,18,20j] but this activity is attributed to the *o*-formyl hydroxy-lactone that is not shared with illudinine. Illudinine and its synthetic precursors showed no LAR inhibitory activity in preliminary assays (not shown).

On the other hand, we recognized certain structural commonalities with the known monoamine oxidase inhibitors (MAOIs) rasagiline and M30 (Figure 3).[40] Rasagiline shares an indane core with illudinine, and M30 is a hydroxy-quinoline, not unlike the methoxy-isoquinoline core of illudinine. Rasagiline and M30 are irreversible submicromolar MAOIs, with rasagiline having selectivity for MAO-B. Therefore, we tested illudinine and its bromo-isoquinoline precursor **11** for MAO-B activity.

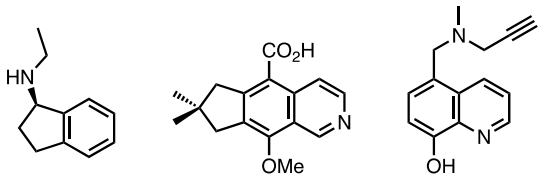


Figure 3. Structural commonalities between illudinine and known MAOIs rasagiline and M30.

Illudinine (**1**) and bromo-isoquinoline **11** were observed to inhibit MAO-B dose-dependently and with similar potency in our preliminary assays (Figure 4). We determined the IC_{50} for illudinine to be 18.3 ± 7.1 μM, whereas bromo-isoquinoline **11** had an IC_{50} of 22.5 ± 2.8 μM in our assays. This is the first biological activity reported for illudinine.

Having observed MAO-B inhibitory activity from illudinine and **11**, we screened a small sample of analogues as potential

MAO-B inhibitors at a concentration of 22 μM. (Figure 5). A few initial structure-activity relationship (SAR) observations

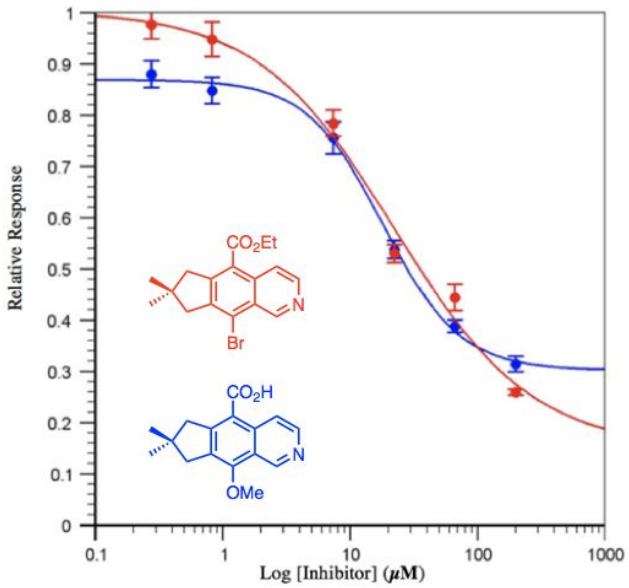


Figure 4. Dose-response curve for illudinine (blue) and bromo-isoquinoline **11** (red) inhibition of human MOA-B.

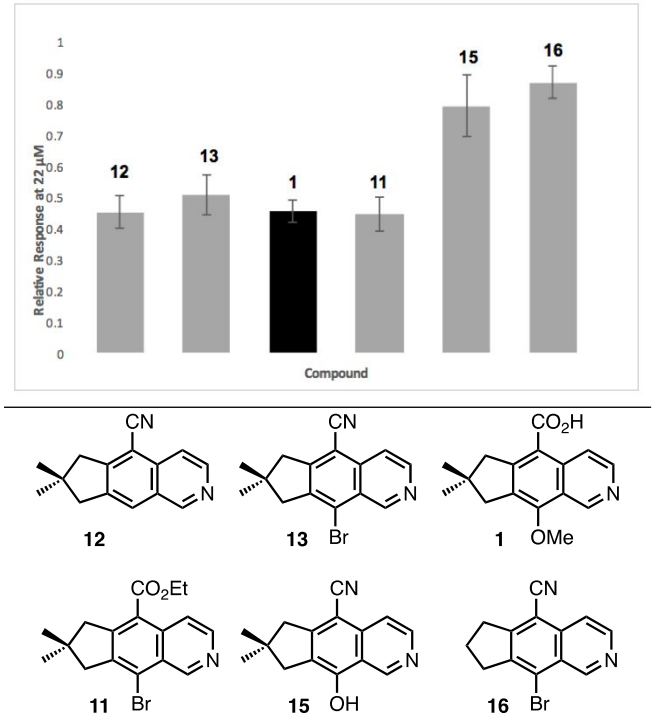


Figure 5. MAO-B inhibitory activity of illudinine and a series of analogues at 22 μM inhibitor concentration.

can be made. Nitriles **12** and **13** and ethyl ester **11** appear to be similar in potency to each other and to illudinine (**1**). Hydroxy-isoquinoline **15** was nearly inactive compared to its bromo- (**13**) or unsubstituted (**12**) isoquinoline counterparts. Deletion of the *gem*-dimethyl substitution on the indane core (compound **16**) was deleterious to activity, which parallels observations made during medicinal chemistry efforts connected to alcyopterosin A[17] and illudalic acid,[18] discussed above in the Introduction section. These preliminary data suggest potential opportunities to improve and refine MAOI activity in future analogues based on the illudinine cores structure.

CONCLUSIONS

We refined our "open and shut" (ring-opening fragmentation and ring-closing oxidative cycloisomerization) approach to the natural product illudinine, completing the total synthesis in 7 steps from dimedone (ca. 55% overall yield). Our first-generation route delivered the natural product in 8 steps and 14–22% overall yield. The key innovation in this new synthesis is the use of the small, linear nitrile functional group as the precursor to the carboxylic acid of illudinine. Illudinine and analogous isoquinolines were observed to have modest inhibitory activity against monoamine oxidase B (MAO-B), which may merit further investigation.

EXPERIMENTAL SECTION

General Experimental Methods. All chemicals were used as received unless otherwise stated. Syringes were used in all protocols requiring the transfer of a liquid reactant of solvent. Tetrahydrofuran (THF) and dichloromethane (DCM) were dried under a column of molecular sieves in an argon atmosphere. A Schleck line was used in all reactions (except for the microwave reactions) to purge reaction vessels and provide an inert, nitrogen atmosphere. A CEM microwave reactor set in constant temperature mode was used for the reactions requiring microwave heating along with the microwave reaction vial, where the temperature was monitored using an external IR sensor and/or internal fiber-optic temperature probe. All purifications were executed using a Biotage Isolera One automated flash column system unless otherwise stated. Yields are reported as isolated yields considered to be ≥95% pure by ^{1}H NMR following flash chromatography. All new compounds were characterized using a JEOL 400 spectrometer to conduct ^{1}H and ^{13}C NMR spectroscopy in $CDCl_3$ (≥99.8 atom % D, contains 0.03% (v/v) TMS) purchased from Cambridge Isotope Laboratories. The chemical shifts (δ) are reported in parts per million (ppm) relative to the $CHCl_3$ peak (7.26 ppm and 77.16 ppm for ^{1}H and ^{13}C, respectively). The coupling constants (J) are reported in Hertz (Hz). Mass spectra were recorded using electrospray ionization (ESI).

Monoamine oxidase assays. Illudinine and analogues were dissolved in 2% dimethyl sulfoxide (DMSO) buffer solution and added with purified MAO-B and kynuramine in a 96-well plate. After 30 minutes of incubation at 37 ºC, a sodium chloride stop solution was added and the plate was analyzed using a plate reader. Excitation-emission fluorescence spectroscopy at 310 and 380 nm was used to determine the enzymatic activity relative to the negative control (no inhibitor added). MAO-B metabolized kynuramine to 4-hydroxyquinoline which can be quantified using fluorescence. A 2% DMSO buffer solution was prepared by mixing 19.6 mL of 0.1 M phosphate solution at pH 7.4 with 0.4 mL of DMSO. The kynuramine substrate solution was made by taking 19.15 μL of 25 mM kynuramine solution and adding it to 5.981 mL of the 2%-DMSO buffer. The MAO-B enzyme solution combines 75 μL of MAO-B with 5.928 mL of buffer. Using this method allow the concentration of DMSO to remain constant in each well. For the dose-response assays. the inhibitor concentration range started at 200 μM and finished at 0.274 μM. IC_{50} values were determined using an online IC_{50} calculator.[41]

(*Z*)-5,5-Dimethyl-2-(pyridin-4-yl)oct-2-en-7-ynenitrile (8b). To a solution of the reduced vinyl triflate **6** (1.17 g, 4.23 mmol, 1.1 equiv.) dissolved in 20 mL of THF at -78 °C, 12.1 mL of lithium (bistrimethylsilyl)amide (1.0 M in THF, 3.1 equiv.) was added dropwise. The solution was stirred for 5 minutes at -78 °C before adding 4-pyridinylacetonitrile hydrochloride (0.600 g, 3.88 mmol, 1.0 equiv.) as a solid. The reaction mixture was stirred for an additional 10 minutes at -78 °C, and was then allowed to come to room temperature. The reaction was stirred at room temperature for 30 minutes and then at 60 °C for 2 hours. The reaction was monitored by TLC using 30% EtOAc in hexanes as the eluent. Upon complete consumption of the starting material, the reaction mixture was cooled to room temperature and quenched with half-saturated ammonium chloride. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum. The product was purified by flash chromatography using a gradient from 10%-60% EtOAc in hexanes to give **8b** (0.790 g, 93%) as a solid; m.p.: 41-42 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.67 (d, J= 4.2Hz, 2H), δ 7.44 (d, J= 6.2Hz, 2H), δ 7.16 (t, J= 8Hz, 1H), δ 2.68 (d, J= 8Hz, 2H), δ 2.21 (d, J= 2.5Hz, 2H), δ 2.09 (t, 3.6Hz, 1H), δ 1.12 (s, 6H). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 150.7, 147.8, 140.5, 119.9, 116.9, 116.2, 115.6, 81.3, 71.4, 43.8, 35.7, 32.0, 27.0. HRMS (ESI+) calculated for $C_{15}H_{16}N_2^+$ [(M+H)$^+$]: 225.1386, found 225.1392.

7,7-Dimethyl-7,8-dihydro-6*H*-cyclopenta[*g*]isoquinoline-5-carbonitrile (12). Enyne **8b** (300 mg, 1.34 mmol) was dissolved in 12 mL of *ortho*-dichlorobenzene in a 35-mL CEM microwave vial. The reaction mixture was stirred and heated to 200 °C by microwave radiation. The temperature was monitored using the (calibrated) IR sensor from the CEM instrument. After 24 hours, the solution was loaded onto a Biotage silica gel column. Three column volumes of hexanes were used to flush out the solvent. The product was purified using a gradient elution from 0-80% ethyl acetate in hexanes. The fractions were combined, and the solvent was removed under reduced pressure to give **12** (252.4 mg, 1.14 mmol, 85%) as a solid; m.p. 85-88 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.22 (s, 1H), δ 8.63 (d, J= 6Hz, 1H), δ 7.92, δ 7.92 (overlapping 2H), δ 3.12 (s, 2H), δ 2.97 (s, 2H), δ 1.25 (s, 6H).^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 155.5, 152.2, 144.8, 144.4, 138.9, 135.0, 127.8, 127.4, 117.6, 116.0, 104.8, 47.6, 47.3, 41.1, 28.3. HRMS (ESI+) calculated for $C_{15}H_{14}N_2^+$ [(M+H)$^+$]: 223.1230, found 223.1230.

9-Bromo-7,7-dimethyl-7,8-dihydro-6*H*-cyclopenta[*g*]isoquinoline-5-carbonitrile (13). Isoquinoline **12** (394.8 mg, 1.78 mmol, 1.0 equiv) was dissolved in 9 mL of concentrated sulfuric acid and stirred at 0° C for 10 minutes. *N*-Bromosuccinimide (695 mg, 3.91 mmol, 2.2 equiv) was added portion-wise over 2 minutes, and the flask was resealed. The reaction was stirred at 0° C for an additional 10 minutes and then at room temperature for 18 hours. The solution was cooled at 0 °C again before diluting carefully with 25 mL of water. The solution was adjusted to pH 8-9 using 30% ammonium hydroxide. The aqueous layer was extracted with ethyl acetate. The organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated. The crude product was purified via flash chromatography using a 7-50% gradient elution of EtOAc in hexanes to give **13** (472 mg, 88%) as a solid; m.p.: 172-175 °C.^{1}H-NMR (400MHz, $CDCl_3$): δ 9.59 (s, 1H), δ 8.72 (d, J= 6Hz, 1H), δ 7.89 (d, J= 5.6Hz, 1H), δ 3.22 (s, 2H), δ 3.02 (s, 2H), δ 1.26 (s, 6H). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 155.0, 151.6, 145.6, 145.5, 136.4, 126.1, 125.0, 117.4, 115.5, 110.2, 104.5, 49.5, 48.8, 40.1, 28.6. HRMS (ESI+) calculated for $C_{15}H_{13}N_2Br^+$ [(M+H)$^+$]: 301.0335, found 301.0335.

9-Methoxy-7,7-dimethyl-7,8-dihydro-6*H*-cyclopenta[*g*]isoquinoline-5-carbonitrile (14). Isoquinoline **13** (103 mg, 0.342 mmol, 1.0 equiv.) was dissolved in 5 mL of anhydrous methanol, and then 30% sodium methoxide (0.761 mL, 3.42 mmol, 10 equiv.) was added. A jacketed condenser was connected to the flask and the solution was refluxed at 65°C for 4 hours. After completion of the reaction was confirmed by TLC, the reaction was cooled to room temperature and diluted with 10 mL of water. HCl (1M, 3 mL) was added dropwise to quench the reaction. The aqueous layer was extracted with ethyl acetate, and the organic layer was washed with water, brine, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified using flash chromatography with a 10-60% gradient elution of ethyl acetate in hexanes to give **14** (80.2 mg, 93%) as a solid; m.p.: 120-123 °C. ^{1}H-NMR (100MHz, $CDCl_3$): δ 9.58 (s, 1H), δ 8.72 (d, J= 6Hz, 1H), δ 7.89 (d, J= 5.6Hz, 1H), δ 3.22 (s, 2H), δ 3.02 (s, 2H), δ 1.26 (s, 6H). ^{13}C{^{1}H}NMR (400 MHz, $CDCl_3$): δ 159.4, 156.6, 147.2, 143.4, 137.1, 128.4, 121.8, 117.8, 116.0, 98.7, 60.6, 47.6, 46.1, 40.8, 28.3. HRMS (ESI+) calculated for $C_{16}H_{16}N_2O^+$ [(M+H)$^+$]: 252.1223, found 252.1216.

Illudinine (1). Isoquinoline **14** (65.0 mg, 0.258 mmol, 1.0 equiv) was dissolved in 6 mL of ethanol, and KOH powder (144.5 mg, 2.58 mmol, 10.0 equiv.) was added quickly to the solution. The solution was heated at reflux for 72 hours before it was allowed to cool to room temperature. The reaction was quenched with 30 mL of pH-7 phosphate buffer. The aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over $MgSO_4$ and concentrated to give 69.1 mg of illudinine (99% yield) as a white powder; m.p.: 220-225 °C. ^{1}HNMR (600 MHz, CD_3OD + 1 drop of TFA): δ 9.72 (s, 1H), 9.01 (d, J = 6.96Hz, 1H), 8.51 (d, J = 6.92Hz, 1H), 4.30 (s, 3H), 3.28 (s, 2H), 3.25 (s, 2H), 1.22 (s, 6H). ^{13}C{^{1}H}NMR (100MHz, CD_3OD + 1 drop of TFA): δ168.6, 163.7, 157.3, 143.4, 139.4, 133.7, 132.9, 123.9, 123.2, 120.8, 61.8, 50.8, 46.3, 41.3, 28.2. HRMS (ESI+) calculated for $C_{16}H_{18}NO_3^+$ [(M+H)$^+$]: 272.1287, found 272.1277.

9-Hydroxy-7,7-dimethyl-7,8-dihydro-6*H*-cyclopenta[*g*]isoquinoline-5-carbonitrile (15). Isoquinoline **13** (100.3 mg, 0.33 mmol, 1.0 equiv.), acetohydroxamic acid (149.9 mg, 1.99 mmol, 6 equiv.), and K_2CO_3, (410.1 mg, 3.33 mmol, 10 equiv.) were dissolved in DMSO (1.1 mL). The brown, heterogeneous solution was allowed to stir overnight at 80 °C. After cooling to room temperature, the solution was placed in an ice bath without stirring where HCl (1 M) was added slowly dropwise to quench the reaction. During the HCl addition the solution formed a yellow tint, and after enough HCl was added the solid, crude product crashed out of solution. The solid was isolated by filtration and purified using flash chromatography (0-10% methanol in DCM) to provide **15** as a bright yellow solid (64.3 mg, 81%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.76 (s, 1H), 8.47 (d, J = 1.5 Hz, 1H), 7.94 (d, J = 1.6 Hz, 1H), 3.10 (s, 2H), 2.92 (s, 2H), 1.24 (s, 6H). ^{13}C{^{1}H}NMR (100 MHz, DMSO-d6): δ158.0, 140.4, 138.4, 135.6, 121.6, 117.9, 114.3, 101.8, 99.5, 93.3, 45.4, 41.0 30.5, 24.6. (ESI+) calculated for $C_{15}H_{14}N_2O^+$ [(M+H)$^+$]: 239.1179, found 239.1171.

9-Bromo-7,8-dihydro-6*H*-cyclopenta[*g*]isoquinoline-5-carbonitrile (16). This didesmethyl analogue of compound **13**

was made by analogy to **13**, starting from 1,3-cyclohexanedione in place of dimedone. 1,3-Cyclohexanedione was converted into 3-hydroxycyclohex-1-en-1-yl trifluoromethanesulfonate (the vinyl triflate analogous to **6**) as reported previously.[42]

(a) By analogy to the preparation of **8b**, 3-hydroxycyclohex-1-en-1-yl trifluoromethanesulfonate[42] (1.75 g, 7.12 mmol, 1.1 equiv.) was dissolved in THF at –78 °C, and lithium (bistrimethylsilyl)amide (20.1 mL, 1.0 M in THF, 3.1 equiv.) was added dropwise. The solution was stirred for 5 minutes at –78 °C before adding 4-pyridinylacetonitrile hydrochloride (1.0 g, 6.5 mmol, 1.0 equiv.) as a solid. The reaction mixture was stirred for an additional 10 minutes at -78 °C, then 30 min at room temperature, and then for 2 h at 60 °C. Workup and purification as described above for compound **8b** provided 1.00 g of a yellow solid, which was tentatively assigned as (*Z*)-2-(pyridin-4-yl)oct-2-en-7-ynenitrile (the didesmethyl analogue of **8b**, 79% yield) and used in the next step.

(b) By analogy to the preparation of **12**, (*Z*)-2-(pyridin-4-yl)oct-2-en-7-ynenitrile as prepared in the previous step (430 mg, 2.19 mmol) was dissolved in 12 mL of *ortho*-dichlorobenzene and heated at 200 °C by microwave radiation with stirring for 24 h. Purification as described for compound **12** provided 322 mg of a yellow solid, which was tentatively assigned as 7,8-dihydro-6*H*-cyclopenta[*g*]isoquinoline-5-carbonitrile (the didesmethyl analogue of **12**, 76% yield) and used in the next step.

(c) By analogy to the preparation of **13**, 7,8-dihydro-6*H*-cyclopenta[*g*]isoquinoline-5-carbonitrile as prepared in the previous step (136 mg, 0.70 mmol) was dissolved in 3 mL of concentrated sulfuric acid and stirred at 0 °C for 10 minutes. *N*-Bromosuccinimide (274 mg, 1.54 mmol, 2.2 equiv) was added in three portions over 2 minutes, and the flask was resealed. The reaction was stirred at 0° C for an additional 1 h and then at room temperature for 12 hours. Workup and purification as described above for compound **13** provided **16** as a white solid (167 mg, 87%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.62 (s, 1H), 8.73 (d, J = 5.6 Hz, 1H), 7.92 (d, 5.6 Hz, 1H), 3.44 (t, J = 7.6 Hz, 2H), 3.23 (t, J = 7.6 Hz, 2H), 2.31 (p, J = 7.6 Hz, 2H). ^{13}C{^{1}H}NMR (100 MHz, $CDCl_3$): δ 155.4, 151.7, 146.2, 145.6, 136.4, 124.7, 117.3, 104.0, 100.1, 34.7, 29.7, 24.1. HRMS (ESI+) calculated for $C_{13}H_{10}BrN_2^+$ 273.0022, found 273.0022

ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra for compounds prepared by the second-generation synthetic route and raw data from the monoamine oxidase inhibition assays (PDF). The Supporting Information is available free of charge on the ACS Publications website.

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ACKNOWLEDGMENT

This work was supported by grants from the National Science Foundation (CHE-1300722 and CHE-1834949). We gratefully acknowledge additional support from West Virginia University and the Eberly Family Foundation. We thank Prof. Brian Miller (Florida State University) for conducting preliminary LAR phosphatase inhibition assays and for helpful discussions.

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Graphical Abstract: