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Letter

Rapid Synthesis of Psychoplastogenic Tropane Alkaloids

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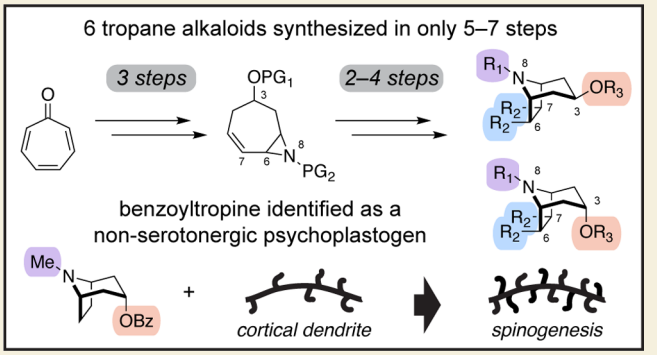
ABSTRACT: Tropane alkaloids are an important class of biologically active small molecules characterized by their 8-azabicyclo[3.2.1]octane core. Because of their numerous medicinal applications, microbial biosynthesis and a variety of chemical syntheses have been designed for individual family members. However, current approaches are not amenable to late-stage structural diversification at N8, C3, C6, or C7, positions that are critical for modulating the biological properties of these molecules. Here, we describe a general approach to the synthesis of tropane alkaloids and their analogues that relies on the construction of the 8-azabicyclo[3.2.1]octane core through aziridination of a cycloheptadiene intermediate, followed by vinyl aziridine rearrangement. Using this strategy, we synthesized six tropane alkaloids and several analogues in only 5−7 steps. Given that the tropane alkaloid scopolamine has been reported to promote structural neuroplasticity and produce antidepressant effects, we tested five tropane-containing compounds for their ability to promote dendritic spine growth in cultured cortical neurons. We found that the orientation of the C3 substituent may play a role in the psychoplastogenic effects of tropane alkaloids. Our work provides a robust platform for producing tropane analogs for future structure−activity relationship studies.



KEYWORDS: *tropane alkaloids, tropacocaine, benzoyltropine, datumetine, total synthesis, aziridine, late-stage functionalization, psychoplastogen*

Since their initial discovery in the early 1800s, over 200 tropane alkaloids have been isolated.[1] These small molecule natural products and their secondary metabolites have served as medicines for over a century.[2,3] The significant biological activity of this class of compounds results from their abilities to modulate numerous targets including monoamine transporters,[4,5] muscarinic receptors,[6] and NMDA receptors,[7] among many others. In 2014, an analysis by Njardarson and co-workers revealed that the tropane core was ranked no. 15 in a list of nitrogen-containing heterocycles most commonly found in FDA-approved drugs,[8] emphasizing the importance of this structural motif in medicine.

The core structural features of these alkaloids include an *N*-methyl-8-azabicyclo[3.2.1]octane core (i.e., tropane) and a hydrophobic tail appended to C3 of the tropane ring (Figure 1A). Crystallographic evidence suggests that the basic nitrogen of tropane alkaloids can form key salt bridges and/or cation−π interactions with various targets, while substituents at C6/C7 and C3 often form hydrogen bonds with neighboring residues.[9−11] We became interested in understanding how the structures of tropane alkaloids might impact their abilities to serve as psychoplastogens, small molecules that promote cortical neuron structural plasticity after a single administration.[12,13] Recent evidence suggests that scopolamine (**6**) is a potent psychoplastogen with the ability to induce spinogenesis in the cortex and produce rapid antidepressant effects.[14,15] Most psychoplastogens studied to date are potent agonists of 5-HT2 receptors.[13,16,17] However, the activity of psychoplastogens such as *N*,*N*-dimethyltryptamine (DMT) and lysergic acid diethylamide (LSD) at 5-HT2A and 5-HT2B receptors limits their therapeutic potential, as activation of these receptors produces hallucinations and cardiac valvulopathies, respectively.[18,19] Given the current drawbacks of serotonergic psychoplastogens, we reasoned that other tropane alkaloids (Figure 1B) might induce structural plasticity similar to that of scopolamine (**6**).

To fully realize the potential of tropane alkaloids and analogues as psychoplastogens, an efficient synthetic strategy enabling late-stage functionalization of N8, C3, C6, and C7 is required. Unfortunately, the microbial production of tropane alkaloids[20] and current chemical syntheses[1] are not amenable to facile diversification at these positions. Historically, many tropane alkaloid syntheses have focused on accessing the

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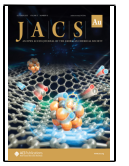

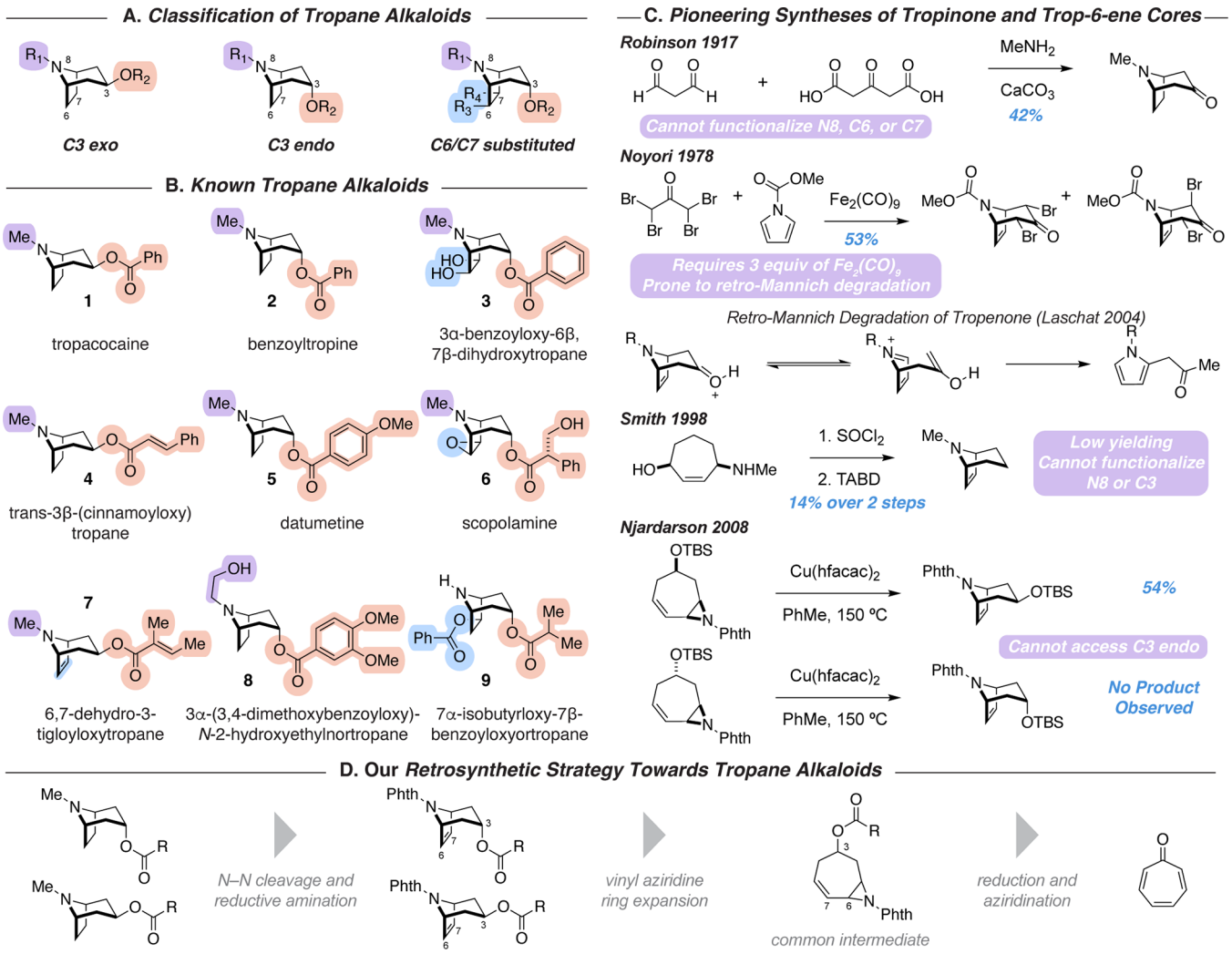

Figure 1. (A) Structural classification of tropane alkaloids. (B) Tropane alkaloids with various substitution patterns at N8, C3, and C6/C7. (C) Previous synthetic strategies to tropane alkaloids and their shortcomings. TABD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene on polystyrene cross-linked with 2% divinylbenzene. (D) Our retrosynthetic strategy for the tropane core enabling late-stage diversification at N8, C3, and C6/C7.

common intermediate tropinone (Figure 1C).[21,22] Unfortunately, the saturated core and *N*-methyl group of tropinone make it unsuitable for accessing scopolamine or more recently isolated tropane alkaloids functionalized at N8, C6, or C7. We reasoned that an N8-protected intermediate possessing a C6–C7 olefin would provide optimal functional group handles to access a range of analogues via late-stage diversification. However, developing a robust, general synthetic strategy for the nortrop-6-ene core has proven challenging. Prior strategies have focused on the formation of the trop-6-ene core with a ketone at the C3 position.[23] Though selective reduction of this C3 ketone could in principle provide access to C3-substituted analogues, a known retro-Mannich degradation pathway hinders further functionalization at the other positions (Figure 1C).[24] Many of these previous strategies have relied on transannular S_N2 reactions, ring closing metathesis, and [4 + 3] cycloadditions between oxyallyl cation precursors and pyrrole derivatives as their key steps, but these approaches suffer from high step counts, low yields, harsh reaction conditions, and/or poor functional group tolerance (Figure 1C).[25−28]

To solve these issues, we were inspired by the work of Njardarson and co-workers (Figure 1C), who demonstrated that the trop-6-ene core could be accessed through Lewis acid catalyzed sigmatropic rearrangement of a vinyl aziridine at elevated temperature (150 °C).[29] Unfortunately, the introduction of functionality at the C3 position led to a drastic decrease in yield for their *syn*-aziridine and complete decomposition of their *anti*-isomer (Figure 1C). We reasoned that if we could overcome this obstacle, we could design a retrosynthesis around diastereomeric phthalimide-protected (Phth) vinyl aziridines that would enable access to both C3-endo and C3-exo trop-6-enes (Figure 1D). These aziridines would be derived from a substituted cycloheptadiene following the selective reduction of tropone and subsequent acylation (Figure 1D). We envisioned that the resulting C6/C7 olefin following vinyl aziridine rearrangement could serve as a functional group handle for accessing analogues substituted at those positions. Moreover, a one-step global reduction/reductive amination sequence seemed to be a viable strategy to rapidly access tropanes that were unfunctionalized at C6/C7. Assuming that we could minimize diastereoselectivity in the aziridination step, this strategy would provide equal access to C3-endo and C3-exo congeners.

We began our synthesis by treating readily available tropone (**10**) with sodium borohydride to afford the requisite 3,5-cycloheptadiene-1-ol **11** in 93% yield (Scheme 1).[30]

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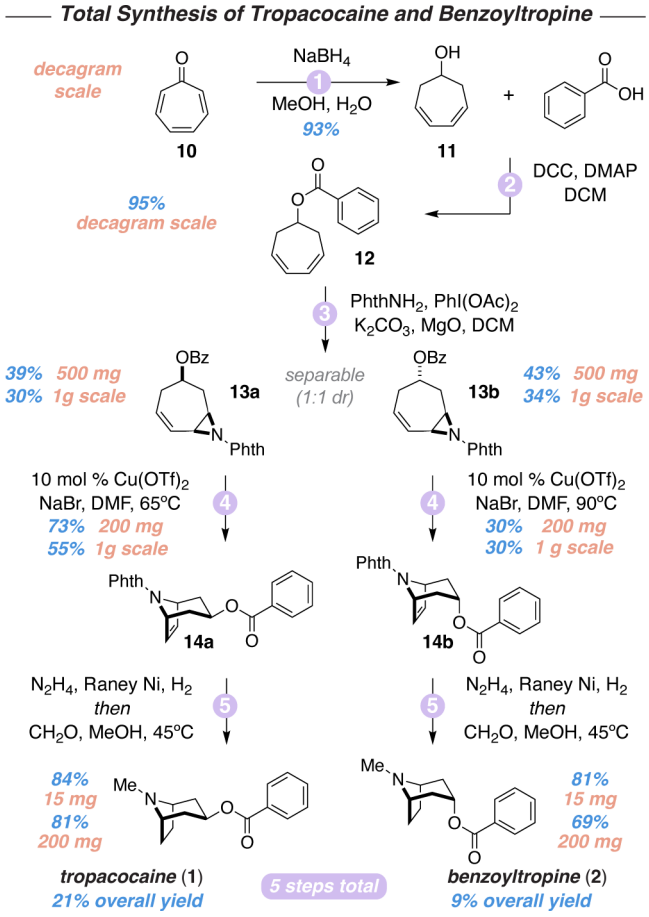
Scheme 1. Total Synthesis of Tropacocaine (1) and Benzoyltropine (2)



Subsequent esterification of **11** proceeded smoothly to give benzoate ester **12** in 95% yield.[31] Both of these reactions could be easily conducted on a decagram scale. Next, we explored the aziridination of the diene under a variety of conditions. Initial aziridination attempts using 2,2,2-trichloroethyl sulfamate as the nitrene source were successful, but the diastereomeric Tces-protected aziridines were inseparable. At this point, we screened several nitrogen sources and various dirhodium catalysts (See Table S1). We observed modest diastereoselectivities when sulfamate nitrene precursors were employed with either achiral or chiral rhodium catalysts, while a carbamate nitrogen source gave no appreciable product. In all cases, we observed chemoselective aziridination with no oxidation at the allylic positions or alpha to the benzoate. Ultimately, metal-free aziridination conditions utilizing *N*-aminophthalimide as the nitrene precursor[32] provided the desired diastereomeric aziridines **13a** and **13b** in excellent yield (82% combined yield, 500 mg scale). Importantly, the reaction exhibited the desired lack of diastereoselectivity, and the products were easily separated via silica gel chromatography, which enabled us to access roughly equal quantities of the precursors to the C3-endo and C3-exo tropanes.

To effect the key vinyl aziridine rearrangement, we first subjected **13a** and **13b** to the conditions described by Njardarson and co-workers[29] (i.e., 5% $Cu(hfacac)_2$, PhMe, 150 °C). Unfortunately, these conditions resulted in limited conversion to **14a** (36% yield) or **14b** (19% yield) with substantial decomposition of the starting material. We explored

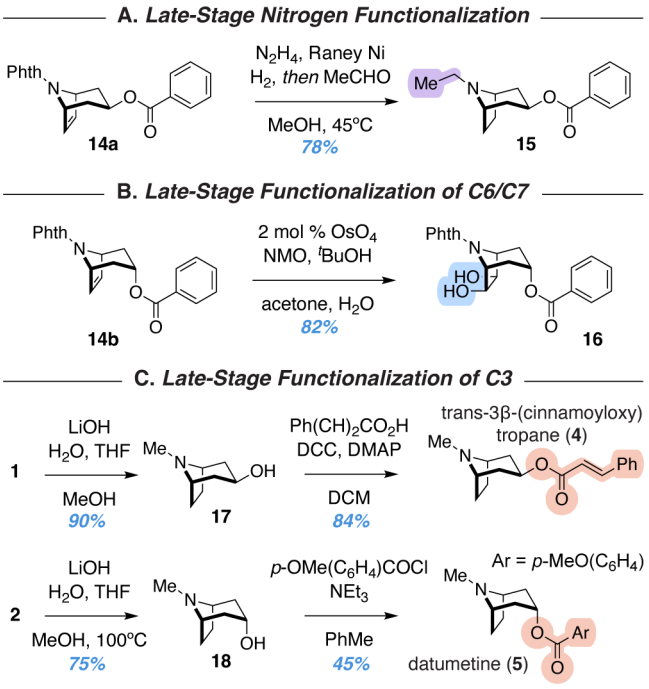


Figure 2. (A) Phthalimide deprotection, olefin reduction, N−N bond cleavage, and reductive amination can be accomplished in a single step to yield N8-functionalized tropanes. (B) Olefin functionalization enables access to tropane analogues substituted at C6/C7. (C) Benzoate hydrolysis followed by esterification enabled the first-ever total synthesis of *trans*-3*β*-(cinnamoyloxy)tropane (**4**) and datumetine (**5**). Hydrolysis of **1** and **2** produced the natural products pseudotropine (**17**) and tropine (**18**), which could be further functionalized to produce the natural products **4** and **5**, respectfully.

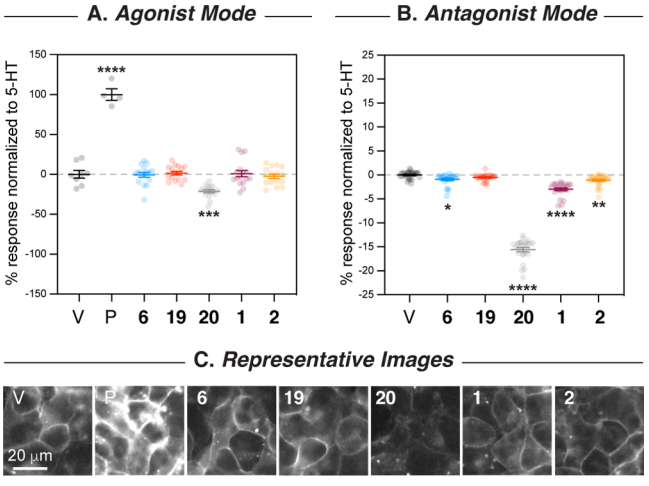


Figure 3. Tropane alkaloids are not agonists of the 5-HT2A receptor. (A) PsychLight assays conducted in agonist mode indicated that tropane alkaloids (treated at 10 μM) are not agonists of 5-HT2A receptors and, thus, have low hallucinogenic potential. (B) PsychLight antagonist mode studies were conducted in the presence of serotonin (100 nM) and experimental compound (10 μM). (C) Representative images of psychLight-expressing HEK293T cells after treatment with compounds in agonist mode. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001, as compared with VEH controls [one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparisons test]. V = vehicle; P = positive control (i.e., serotonin).

a variety of strategies to optimize the vinyl aziridine rearrangement, including Lewis acid, radical relay, and

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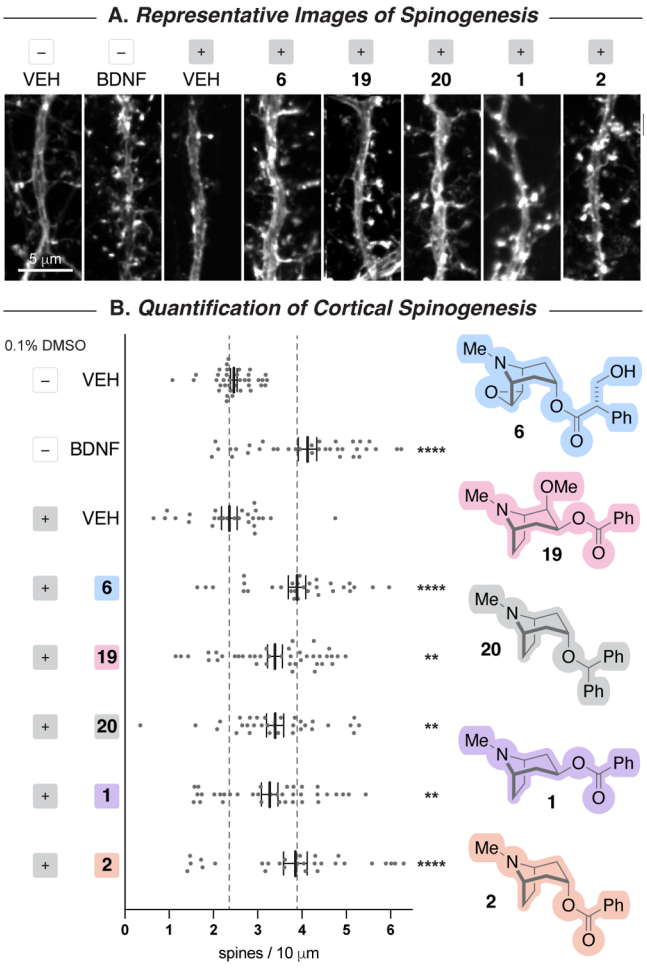

Figure 4. Tropane alkaloids possess psychoplastogenic properties. (A) Representative images of cortical neurons (DIV 21) treated with compounds (10 μM) for 24 h. Neuronal morphology was visualized using phalloidin conjugated to AlexaFluor 488. Brain-derived neurotrophic factor (BDNF) was used as a positive control (50 ng/mL). Treatments with and without 0.1% DMSO are indicated with + and − symbols, respectively. Dotted lines indicate the level of spinogenesis induced by VEH and positive (scopolamine) controls with 0.1% DMSO. (B) Quantification of the spinogenesis assays. Data are presented as mean ± standard error of the mean. Individual data points indicate spines counted on secondary branches from individual neurons across 3 independent culture preparations. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$, as compared with VEH controls [one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparisons test]. VEH = vehicle.

photoredox catalysis, though none of these strategies proved fruitful (Table S2). Fortunately, we discovered that an S_N2'/S_N2 cascade sequence at elevated temperature yielded the desired bicyclic ring systems in reasonable yields. However, we noticed that **14a** and **14b** were quite sensitive to high temperatures, leading to a faster rate of decomposition. Ultimately, we found that a combination of NaBr and an azaphilic Cu(II) catalyst proved to be the best conditions for vinyl aziridine rearrangement, as this enabled the reactions to be conducted at lower temperatures avoiding decomposition and de-esterification of the benzoate. While **13a** was converted to **14a** in high yields (55−73%), the conversion of **13b** to **14b** proved to be more challenging, presumably due to the C3 substituent blocking nucleophilic attack on the vinyl aziridine.

To complete the syntheses of tropacocaine (**1**) and benzoyltropine (**2**), we subjected **14a** or **14b** to sequential addition of hydrazine, Raney Ni, and formaldehyde under a hydrogen atmosphere, which enabled phthalimide deprotection, hydrazine cleavage, olefin reduction, and mono-*N*-methylation to occur in a single reaction vessel in high yields (81−84%). Hydrazine cleavage of the phthalimide was essential, as all attempts to reduce the N−N bond prior to deprotection failed. This 5-step route gave tropacocaine (**1**) and benzoyltropine (**2**) in 21% and 9% overall yields, respectively (Scheme 1). Prior to our work, there was only a single total synthesis of tropacocaine[33] and no de novo total syntheses of benzyoyltropine reported in the literature. Our strategy relying on the production of vinyl aziridines **13a** and **13b** from **12** resulted in the shortest and highest yielding synthesis of tropacocaine (**1**) and the first total synthesis of benzoyltropine (**2**). Importantly, this strategy gave us access to several other tropane natural products and analogues through late-stage diversification (Figure 2).

To explore the versatility of this synthetic strategy for accessing N8-, C6/C7-, and C3-substituted tropanes, we synthesized four additional tropane natural products and two tropane analogues (Figure 2). Nitrogen ethylation was achieved in excellent yield (78%) in a single reaction vessel by subjecting **14a** to a multistep transformation involving phthalimide deprotection, N−N bond cleavage, olefin reduction, and reductive amination with acetaldehyde (Figure 2A). To access the C6/C7-substituted analogue **16**, we treated trop-6-ene **14b** with catalytic OsO_4 and *N*-methylmorpholine-*N*-oxide (NMO), which yielded the desired product in 82% yield (Figure 2B). Finally, we completed the first-ever total synthesis of *trans*-3β-(cinnamoyloxy)tropane (**4**) and datumetine (**5**) following ester hydrolysis and acylation of **1** and **2**, respectively (Figure 2C). Hydrolysis of **1** and **2** provided their respective alcohols **17** and **18** in 90% and 75% yield, respectively. Treating pseudotropine **17** with *trans*-cinnamic acid in the presence of DCC or treating tropine **18** with *p*-anisoyl chloride in the presence of triethylamine led to the production of *trans*-3β-(cinnamoyloxy)-tropane (**4**) and datumetine (**5**) in 84% and 45% yield, respectively. With this synthetic strategy, we can perform late-stage functionalization reactions at four separate positions on the tropane scaffold with minimal increases in step count (0−2 additional steps) from our 5-step syntheses of tropacocaine (**1**) and benzoyltropine (**2**).

With an efficient synthesis of **1** and **2**, we were able to easily produce quantities suitable for biological evaluation. We focused on assessing their abilities to serve as non-serotonergic psychoplastogens, and we directly compared their effects to the tropane alkaloids scopolamine (**6**) and cocaine (**19**), as well as the tropane-containing medication benztropine (**20**). To determine if these tropane-containing compounds possess any activity at 5-HT2A receptors, we utilized psychLight, a 5-HT2A receptor-based biosensor capable of predicting the hallucinogenic potential of 5-HT2A receptor ligands in animal models.[34] In agonist mode, only the positive control serotonin activated the biosensor, with **20** exhibiting some degree of inverse agonism (Figure 3A). Negligible changes in psychLight fluorescence were observed in antagonist mode with the exception that **20** produced a strong antagonist signal consistent with previous results.[34] Taken together, these studies suggest that the tropane alkaloids tested here have

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minimal to no activity at 5-HT2A receptors, making them interesting candidates as non-serotonergic psychoplastogens.

To assess the ability of tropane alkaloids to induce structural neuroplasticity, we treated mature cortical cultures (DIV 20) with compounds (10 μM) for 24 h and then assessed spinogenesis via confocal microscopy. All five tropane-containing compounds tested promoted dendritic spine growth compared to the vehicle control (Figure 4). However, scopolamine (**6**) and benzoyltropine (**2**) exhibited the greatest effect size, which was comparable to that of the positive control brain-derived neurotropic factor (BDNF). Given that both **6** and **2** possess C3-endo substituents, this configuration might be important for maximizing psychoplastogenic effects. However, additional structure−activity relationship studies are necessary to validate that hypothesis. Our work suggests that tropane-containing molecules have the potential to serve as cortical psychoplastogens that do not directly activate 5-HT2A receptors.

In summary, we have developed an efficient synthetic strategy toward tropane alkaloids with four major points of late-stage functionalization. During the development of this synthetic strategy, we achieved 5-step total syntheses of tropacocaine (**1**) and benzoyltropine (**2**) and 7-step total syntheses of *trans*-3β-(cinnamoyloxy)-tropane (**4**) and datumetine (**5**) relying on a vinyl aziridine rearrangement to construct the key trop-6-ene intermediates **14a** and **14b**. Furthermore, we found that benzoyltropine (**2**) was a non-serotonergic psychoplastogen with comparable effects on cortical dendritic spine growth as the muscarinic antagonist and deliriant scopolamine (**6**). Unlike scopolamine (**6**), benzoyltropine (**2**) lacks high affinity for muscarinic receptors suggesting that it might serve as tropane-based psychoplastogen with lower potential for inducing unwanted deliriant side effects.[35]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.3c00472.

Detailed synthetic procedures, and experimental data for all compounds, and ^{1}H and ^{13}C NMR spectra (PDF)

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Author Contributions

WLC performed all of the chemistry. MAG performed the psychLight assays. MAG and AAA performed spinogenesis assays with assistance from WLC. DEO conceived the project. DEO and WLC wrote the manuscript with input from all authors.

Notes

The authors declare the following competing financial interest(s): DEO is a co-founder of Delix Therapeutics, Inc., serves as the chief innovation officer and head of the scientific advisory board, and has sponsored research agreements with Delix Therapeutics. Delix has licensed technology from UC Davis related to analogues of tropane alkaloids. The sponsors of this research were not involved in the conceptualization, design, decision to publish, or preparation of the manuscript.

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