Discovery and Total Synthesis of a Bis(Cyclotryptamine) Alkaloid Bearing the Elusive Piperidinoindoline Scaffold

Jordan J. Dotson, J. Logan Bachman, Miguel A. Garcia-Garibay*, and Neil K. Garg*

Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095, United States

ABSTRACT: Bis(cyclotryptamine) alkaloids have been popular topics of study for many decades. Five possible scaffolds for bis(cyclotryptamine) alkaloids were originally postulated in the 1950s, but only four of these scaffolds have been observed in natural products to date. We describe synthetic access to the elusive fifth scaffold, the piperidinoindoline, through syntheses of compounds now termed "dihydropsychotriadine" and "psychotriadine." The latter of these compounds was subsequently identified in extracts of the flower *Psychotria colorata*. Our synthetic route features a stereospecific solid-state photodecarbonylation reaction to introduce the key vicinal quaternary stereocenters.

Since the initial isolation of calycanthine in 1888,[1] bis(cyclotryptamine) alkaloids[2] have captivated the attention of scientists worldwide. Interest in these natural products has been fueled by a combination of their biological activities and intricate structures. With regard to the latter, the identification and structural elucidation of bis(cyclotryptamine) alkaloids has a rich history.[2a,b] For example, although calycanthine was isolated in 1888, its structure remained a mystery until 1954, when Robert Robinson and H. J. Teuber first proposed a plausible structural identity.[3] At that time, they suggested the existence of five possible distinct ring systems, depicted as **1**–**5**, arising from common biosynthon **6** (Figure 1). On the basis of degradation studies, piperidinoindoline **5** was postulated as the constitutional isomer for calycanthine. However, in 1960, studies by Woodward[4] and Hamor[5] identified bridged bicycle **1** as the correct structure.

Over the subsequent six decades, many isolation reports,[6] biosynthetic studies,[7] and synthetic efforts have been disclosed.[2] This has led to the discovery of more than 20 bis(cyclotryptamine) alkaloids to date.[2] Interestingly, of the five possible isomeric scaffolds originally proposed, only four have been confirmed to exist (i.e., **1**–**4**) in isolated natural products.[6] With regard to synthetic studies, completed total syntheses of natural products bearing scaffolds **1**, **2**, and **4** have been most common over the past few decades. Efforts to access piperidinoindoline scaffold **5** have been rare. In a seminal study, Scott and coworkers are believed to have accessed a compound bearing scaffold **5** in 1967.[8] More recently, compounds bearing substituted piperidinoindoline scaffolds have been accessed in the context of communesin studies, as shown independently by our and Tang's group[9] and by Movassaghi's group.[10] Scaffold **5** has not been observed naturally.

Like many laboratories, we have been drawn to the bis(cyclotryptamine) alkaloids due to their remarkable structures. These compounds typically feature four nitrogen atoms, vicinal quaternary stereocenters (arising biosynthetically from the dimerization of a tryptamine derivative[2a–c,7]), and six interwoven rings. With the aim of potentially accessing the various isomeric members of the family, we targeted biosynthon **6**. Overman,[11] Movassaghi,[12] and others,[2,13] have elegantly demonstrated the success of this general approach to access pyrrolidinoindoline isomer **2** from pre-formed indoline (or related) ring systems.[14] In this manuscript, we demonstrate an alternative approach to **6** that relies on the stereospecific photodecarbonylation of a crystalline ketone to access the requisite vicinal quaternary centers, ultimately leading to the synthesis of an alkaloid bearing the elusive piperidinoindoline scaffold **5** and its identification in *Psychotria colorata* flower extracts.

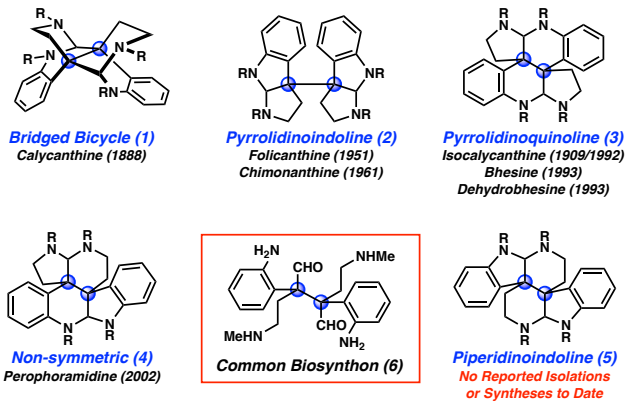
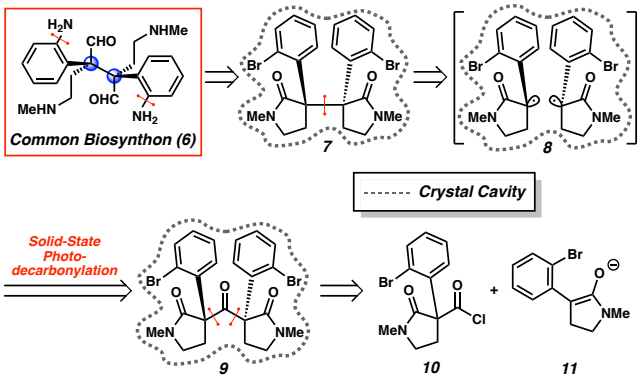


Figure 1. Possible bis(cyclotryptamine) alkaloid constitutional isomers **1**–**5** arising from common biosynthon **6**.

Our retrosynthetic approach targeted biosynthon **6** as a potential means to access various bis(cyclotryptamine) scaffolds (Scheme 1). As **6** itself would not be isolable, we targeted a synthetic equivalent or congener by reduction of bis(lactam) **7** and late-stage C–N bond formation. In turn, brominated compound **7** would arise from ketone **9** via a solid-state photodecarbonylation reaction. This key step would proceed by Norrish type I photodecarbonylation of **9**, followed by

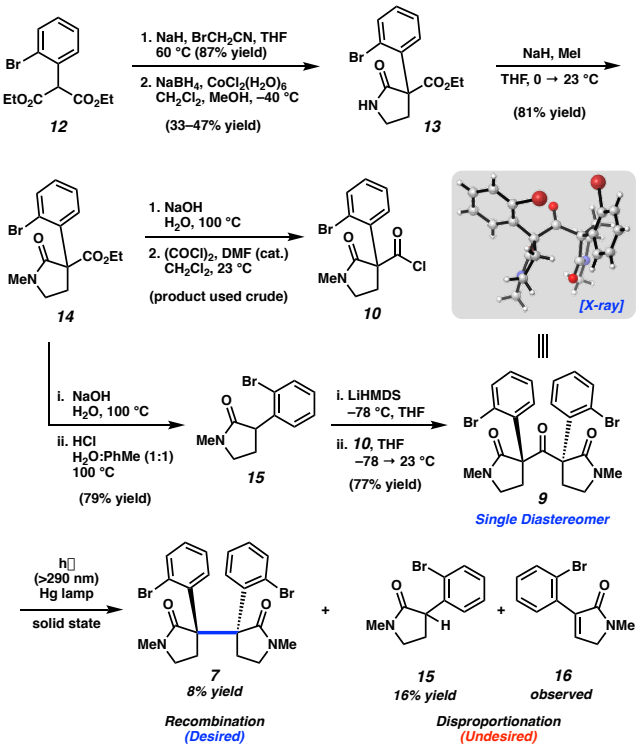
coupling of radical pair **8**. Due to conformational restrictions imposed by the rigid reaction cavity of the crystal lattice, illustrated by the dotted lines, the conversion of **9** to **7** was expected to occur with retention of stereochemistry. We have previously shown the success of such solid-state photodecarbonylation reactions in simpler systems.[15,16,17] Moreover, this key step would complement the elegant radical-based approach to accessing cyclotryptamine alkaloids pioneered by Movassaghi and coworkers.[12] Ketone **9** would be prepared from acid chloride **10** and enolate **11**.[18]

Scheme 1. Retrosynthetic analysis of biosynthon **6** with key stereospecific radical combination in the crystalline state.



Scheme 2 summarizes our synthesis of ketone substrate **9** and the attempted photodecarbonylation reaction. Arylmalonic ester **12** was converted to pyrrolidinone **13** through alkylation with bromoacetonitrile followed by a reductive cyclization. Subsequent methylation furnished pyrrolidinone **14**, which served as a point of divergence. In one pathway, **14** was converted to acid chloride **10** through a two-step sequence involving saponification and treatment of the resultant carboxylic acid with oxalyl chloride and catalytic DMF. In the other sequence, **14** was saponified and then thermally decarboxylated to provide amide **15** in 79% yield. To unite the fragments, amide **15** was converted to its lithium enolate by deprotonation with LiHMDS. In situ trapping with acid chloride **10** delivered ketone **9**, the desired substrate for photodecarbonylation, as validated by X-ray crystallography.[19] Of note, only the *d,l*-diastereomer of **9** was observed, which we attribute to a highly ordered transition state mediated by Li^+ chelation, given prior literature reports.[16b] With crystalline substrate **9** in hand, we attempted the key solid-state photodecarbonylation. However, only a small quantity of the desired product **7** was formed. Instead, the mass balance was attributed to competitive disproportionation, giving products **15** and **16**, as well as substantial non-specific decomposition.[20] Although the yield of **7** was low, thus limiting late-stage efforts, the formation of **7** served as a proof-of-principle that a solid-state photodecarbonylation could forge the critical vicinal quaternary stereocenters with easily modifiable functional groups in place on the aromatic rings.

Scheme 2. Synthesis and photodecarbonylation of ketone **9**.



To improve the efficiency of the photodecarbonylation reaction, we explored structural derivatives of ketone substrate **9**. Our most promising findings are shown in Figure 2.[17] In four linear steps, pyrrolidinone **13** was converted to ketone **17**, bearing removable *para*-methoxybenzyl (PMB) protecting groups (Figure 2A, see SI for details). With the hope of being able to introduce other *N*-substituents and identify a crystalline substrate, we then attempted to enact oxidative cleavage of the PMB moieties using ceric ammonium nitrate (CAN). However, this led to the formation of imide products **18** and **19**. Given that both compounds were high-melting crystalline solids, we tested them in the solid-state photodecarbonylation reaction (Figure 2B). Whereas symmetrical ketone **18** proved completely unreactive, even under prolonged irradiation, we were delighted to find that hemiacyl ketone **19** underwent the desired reaction to furnish **21** after *N*-deprotection. Of note, despite going through the intermediacy of a radical pair with no configurationally inert stereocenters, this decarbonylative C–C bond forming reaction proceeded with high diastereoselectivity and established the vicinal quaternary stereocenters present in biosynthon **6**.[16c,21]

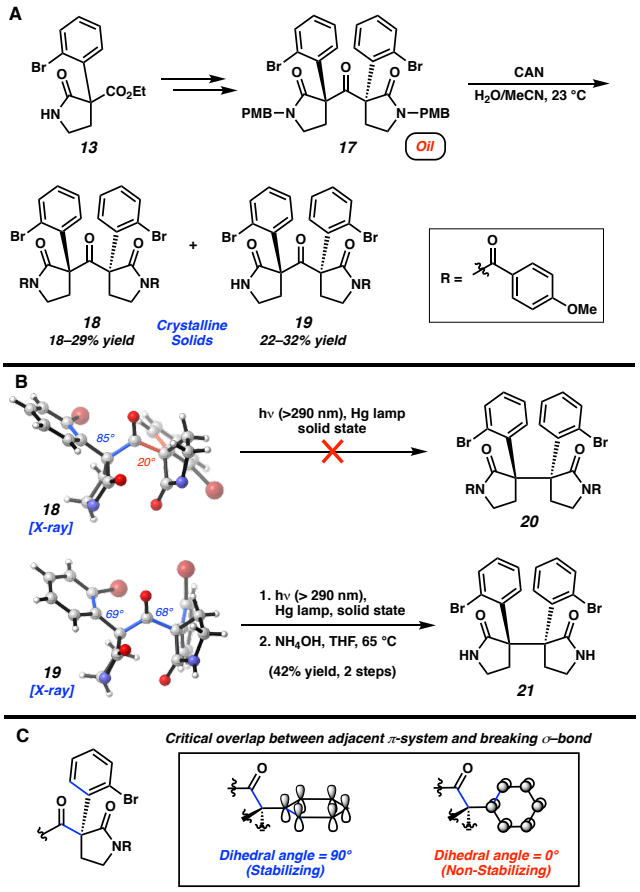
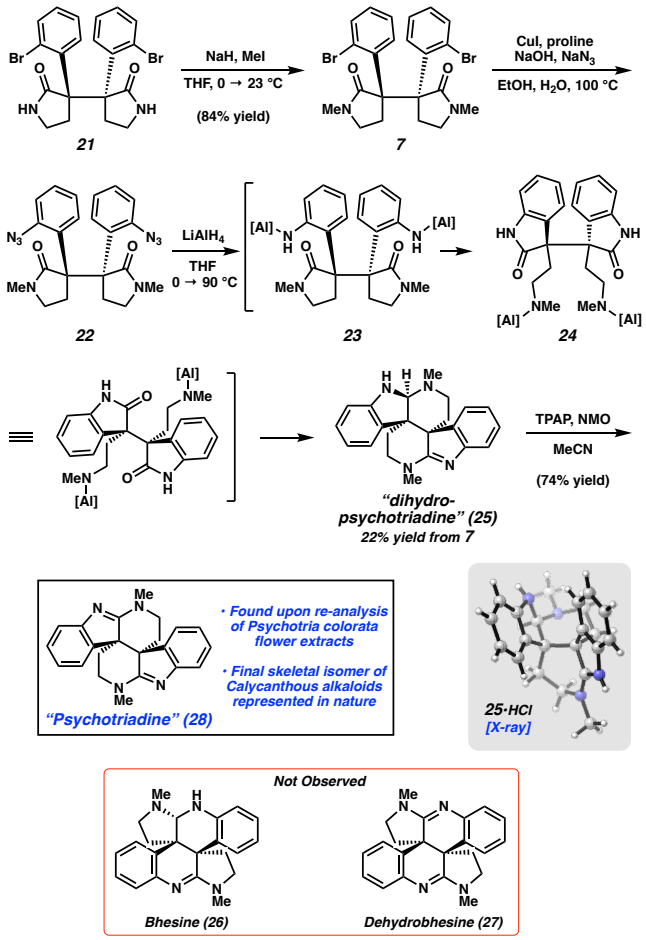


Figure 2. Preparation of substrates **18** and **19**, solid-state photodecarbonylation studies, and explanation for reaction outcomes (the R groups on imides **18** and **19** are removed from the X-ray renderings for clarity).

The dramatically different reactivities of ketones **18** and **19** can be rationalized based on the analysis shown in Figure 2C and inspection of the single crystal X-ray structures (see Figure 2B)[19] for both compounds. Solid-state photodecarbonylation requires stabilization of the breaking C–C sigma bonds by neighboring π-systems.[15,22] The extent of these hyperconjugative interactions in substrates **18** and **19** can be correlated to the dihedral angle between the breaking C–C sigma bond and the nearest C–C bond of the aromatic π-system (see bonds highlighted in blue in Figure 2C). A dihedral angle of 90° is ideal, allowing for maximum orbital overlap. Alternatively, if the dihedral angle is 0°, the C–C sigma bond and π-system will be orthogonal, resulting in no electronic stabilization. In considering ketone **18**, the two relevant dihedral angles are 85° and 20°, the latter of which presumably leads to negligible orbital overlap and failed bond homolysis. On the other hand, the relevant dihedral angles in ketone **19** are 69° and 68°, which we surmise provide sufficient orbital overlap to facilitate decarbonylation.

Having installed the key vicinal quaternary stereocenters, we turned our attention to the elaboration of **21** to a bis(cyclotryptamine) alkaloid (Scheme 3). *N*-Methylation of **21** proceeded smoothly to furnish **7** in 84% yield. Next, several attempts to effect double C–N bond formation were put forth, but most were deemed unsuccessful, presumably due to the highly sterically hindered nature of the C–Br bonds in **7**. Eventually, we found that a modification of Ma's copper-catalyzed azidation procedure could be implemented to furnish bis(azide) **22**.[23] Bis(azide) **22** could not be isolated cleanly, despite significant effort, and had to be used directly in the subsequent step.[24] With the requisite nitrogen atoms installed, we then attempted a challenging reduction cascade by treating **22** with $LiAlH_4$ at 90 °C. To our surprise, this led to the formation of **25** bearing the elusive piperidinoindoline scaffold.[25,26] The structure of **25**, a compound we have termed "dihydropsychotriadine," was ultimately confirmed by single crystal X-ray diffraction.[19] Interestingly, bhesine (**26**), or variants thereof, were not observed. One plausible pathway from **22** to **25** involves double azide reduction to furnish intermediate **23**, double 5-exo-trig cyclization / transamidation to give **24**, double cyclization to give the piperidine rings,[27] and mono amidine reduction.[28] Despite the mechanistic possibilities for the formation of other isomers (e.g. scaffolds **1**–**4**) during the reduction of **22**, we did not observe any major byproducts by ^{1}H NMR analysis. However, the formation of other isomeric products cannot be ruled out at this time.

Scheme 3. Total synthesis of "psychotriadine" (**28**) bearing the piperidinoindoline scaffold (the chloride counterion of the X-ray structure of **25** is omitted for clarity).



Prior to unambiguously establishing the structure of **25** by X-ray diffraction, we had surmised that **25** could be an aminal stereoisomer of bhesine (**26**). As such, **25** was treated under Ley–Griffith oxidation conditions to ablate the aminal stereo-

center.[29] The product, which we obtained in 74% yield, was compared to an authentic sample of dehydrobhesine (**27**) obtained from the extracts from *Psychotria colorata*.[6a] Although our synthetic sample did not match **27**, the isolation sample also contained a previously unidentified compound representing ~10% of the sample mass. This compound was found to spectroscopically match our synthetic oxidation product. On the basis of crystallographic characterization of **25** and NMR analysis of the oxidation product, we propose the depicted piperidinoindoline structure for compound **28**. Because of its presence in the extracts from *Psychotria colorata*, **28** is presumed to be a naturally occurring metabolite that we have now termed "psychotriadine."[30]

In summary, we have developed a synthetic route to access "psychotriadine," a previously unknown bis(cyclotryptamine) alkaloid bearing the elusive piperidinoindoline scaffold. Our approach features a stereospecific solid-state photodecarbonylation reaction to convert fully substituted ketone substrate **19** into **21** bearing vicinal quaternary stereocenters. The success or failure of this key step correlates to the solid-state geometry of the ketone substrate. Following late-stage C–N bond formation and a reduction cascade, the piperidinoindoline framework could be accessed. Re-analysis of *Psychotria colorata* flower extracts revealed the presence of "psychotriadine," suggesting it is likely a naturally occurring alkaloid. These studies not only underscore the value of solid-state photodecarbonylation chemistry in total synthesis, but also demonstrate that all five of the distinct bis(cyclotryptamine) alkaloid frameworks originally proposed are represented in nature.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Detailed experimental procedures and compound characterization data (PDF)

Data for **9** (CIF)
Data for **18** (CIF)
Data for **19** (CIF)
Data for **25** (CIF)

AUTHOR INFORMATION

Corresponding Author

* mgg@chem.ucla.edu
* neilgarg@chem.ucla.edu

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

The authors thank the National Science Foundation (CHE-1855342 for M.G.G.) and the Trueblood Family (for N.K.G.) for financial support. J.J.D. acknowledges the UCLA Graduate Division for a Dissertation Year Fellowship. We thank Professor Mohammad Movassaghi (MIT) for insightful discussions, Ieva Liepuoniute (UCLA) for computing the relative energies of isomers **27** and **28**, Dr. Saeed Khan (UCLA) for X-ray analysis, and Professor Luisella Verotta (University of Milan, Italy) for helpful discussions and for providing authentic samples of **27** and **28**. These studies were supported by shared instrumentation grants from the NSF (CHE-1048804) and the National Center for Research Resources (S10RR025631).

REFERENCES

[1] Eccles, R. G. Calycanthine. *Druggists' Circular and Chemical Gazette* **1888**, *32*, 65.
[2] For reviews, see: (a) May, J. A.; Stoltz, B. The Structural and Synthetic Implications of the Biosynthesis of the Calycanthaceous Alkaloids, the Communesins, and Nomofungin. *Tetrahedron* **2006**, *62*, 5262–5271. (b) Schmidt, M. A.; Movassaghi, M. New Strategies for the Synthesis of Hexahydropyrroloindole Alkaloids Inspired by Biosynthetic Hypotheses. *Synlett* **2008**, 313–324. (c) Steven, A.; Overman, L. E. Total Synthesis of Complex Cyclotryptamine Alkaloids: Stereocontrolled Construction of Quaternary Carbon Stereocenters. *Angew. Chem., Int. Ed.* **2007**, *46*, 5488–5508. (d) Trost, B. M.; Osipov, M. Recent Advances on the Total Synthesis of Communesin Alkaloids and Perophoramidine. *Chem. Eur. J.* **2015**, *21*, 16318–16343. (e) Xu, J.-B.; Cheng, K.-J. Studies on the Alkaloids of the Calycanthaceae and Their Syntheses. *Molecules* **2015**, *20*, 6715–6738.
[3] (a) Robinson, R.; Teuber, H. J. Reactions with Nitrosodisulfonate. IV. Calycanthine and Calycanthidine. *Chem. Ind. (London)* **1954**, 783–784. (b) Manske, R. H. The Alkaloids of Calycanthacaea. *Alkaloids* **1965**, *8*, 581–589.
[4] Woodward, R. B.; Yang, N. C.; Katz, T. J.; Harley-Mason, J.; Ingelby, R. F.; Sheppard, N. Calycanthine: The Structure of the Alkaloid and Its Degradation Product, Calycanine. *Proc. Chem. Soc., London* **1960**, 76–78.
[5] Hamor, T. A.; Robertson, J. M.; Shrivastava, H. N.; Silverton, J. V. The Structure of Calycanthine. *Proc. Chem. Soc., London* **1960**, 78–80.
[6] For select examples of bis(cyclotryptamine) alkaloid isolations, see: (a) Verotta, L.; Pilati, T.; Tató, M.; Elisabetsky, E.; Amaor, T. A.; Nunes, D. S. Pyrrolidinoindoline Alkaloids from *Psychotria colorata*. *J. Nat. Prod.* **1998**, *61*, 392–396. (b) Balayer, A.; Sévenet, T.; Schaller, H.; Haudi, A. H. A.; Chiaroni, A.; Riche, C.; Païs, M. Dihydroquinoline-Type Alkaloids from *Bhesea paniculate*, *celastraceae*. *Nat. Prod. Lett.* **1993**, *2*, 61–67. (c) Adjibade, Y.; Weniger, B.; Quirion, J. C.; Kuballa, B.; Cabalion, P.; Anton, R. Dimeric Alkaloids from *Psychotria forsteriana*. *Phytochemistry* **1992**, *31*, 317–319. (d) Verbitski, S. M.; Mayne, C. L.; Davis, R. A.; Concepcion, G. P.; Ireland, C. M. Isolation, Structure Determination, and Biological Activity of a Novel Alkaloid, Perophoramidine, from the Philippine Ascidian *Perophoranamei*. *J. Org. Chem.* **2002**, *67*, 7124–7126. (e) Gordin, H. M. On the Crystalline Alkaloid of Calycanthus Glaucus. Third Paper. –On Isocalycanthine, Isomeric with Calycanthine. *J. Am. Chem. Soc.* **1909**, *31*, 1305–1312.
[7] Kirby, G. W.; Shah, S. W.; Herbert, E. J. Biosynthesis of Chimonanthine from [2-^{3}H]Tryptophan and [2-^{3}H]Tryptamine. *J. Chem. Soc. C* **1969**, 1916–1919.
[8] Hall, E. S.; McCapra, F.; Scott, A. I. Biogenetic-Type Synthesis of the Calycanthaceous Alkaloids. *Tetrahedron* **1967**, *23*, 4131–4141.

[9] Lin, H.-C.; McMahon, T. C.; Patel, A.; Corsello, M.; Simon, A.; Xu, W.; Zhao, M.; Houk, K. N.; Garg, N. K.; Tang, Y. P450-Mediated Coupling of Indole Fragments to Forge Communesin and Unnatural Isomers. *J. Am. Chem. Soc.* **2016**, *138*, 4002–4005.

[10] Pompeo, M. M.; Cheah, J. H.; Movassaghi, M. Total Synthesis and Anti-Cancer Activity of All Known Communesin Alkaloids and Related Derivatives. *J. Am. Chem. Soc.* **2019**, *141*, 14411–14420.

[11] For select studies from the Overman group pertaining to **1** and **2**, see: (a) Link, J. T.; Overman, L. E. Stereocontrolled Total Synthesis of *meso*-Chimonanthine and *meso*-Calycanthine via a Novel Samarium Mediated Reductive Dialkylation. *J. Am. Chem. Soc.* **1996**, *118*, 8166–8167. (b) Overman, L. E.; Paone, D. V; Stearns, B. A. Direct Stereo- and Enantiocontrolled Synthesis of Vicinal Stereogenic Quaternary Carbon Centers. Total Synthesis of *meso*- and (–)-Chimonanthine and (+)-Calycanthine. *J. Am. Chem. Soc.* **1999**, *121*, 7702–7703. (c) Overman, L. E.; Larrow, J. F.; Stearns, B. A. Enantioselective Construction of Vicinal Stereogenic Quaternary Centers by Dialkylation; Practical Total Synthesis of (+)- and *meso*-Chimonanthine. *Angew. Chem., Int. Ed.* **2000**, *39*, 213–215. (d) Hoyt, S. B.; Overman, L. E. Investigation of a Dialkylation Approach for Enantioselective Construction of Vicinal Quaternary Stereocenters. *Org. Lett.* **2000**, *2*, 3241–3244. (e) Lebsack, A. D.; Link, J. T.; Overman, L. E.; Stearns, B. A. Enantioselective Total Synthesis of Quadrigemine C and Psycholeine. *J. Am. Chem. Soc.* **2002**, *124*, 9008–9009. (f) Overman, L. E.; Peterson, E. A. Enantioselective Total Synthesis of the Cyclotryptamine Alkaloid Idiospermuline. *Angew. Chem., Int. Ed.* **2003**, *42*, 2525–2528. (g) Kodanko, J. J.; Overman, L. E. Enantioselective Total Synthesis of the Cyclotryptamine Alkaloids Hodgkinsine and Hodgkinsine B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2528–2531. (h) Ellis, J. M.; Overman, L. E.; Tanner, H. R.; Wang, J. A Versatile Synthesis of Unsymmetrical 3,3'-Bioxindoles: Stereoselective Mukaiyama Aldol Reactions of 2-Siloxyindoles with Isatins. *J. Org. Chem.* **2008**, *73*, 9151–9154. (i) Canham, S. M.; Hafensteiner, B. D.; Lebsack, A. D.; May-Dracka, T. L.; Nam, S.; Stearns, B. A.; Overman, L. E. Stereocontrolled Enantioselective Total Synthesis of the [2+2] Quadrigemine Alkaloids. *Tetrahedron* **2015**, *71*, 6424–6436.

[12] For select studies from the Movassaghi group pertaining to **1** and **2**, see: (a) Movassaghi, M.; Schmidt, M. A. Concise Total Synthesis of (–)-Calycanthine, (+)-Chimonanthine, and (+)-Folicanthine. *Angew. Chem., Int. Ed.* **2007**, *46*, 3725–3728. (b) Movassaghi, M.; Schmidt, M. A.; Ashenhurst, J. A. Concise Total Synthesis of (+)-WIN 64821 and (–)-Ditryptophenaline. *Angew. Chem., Int. Ed.* **2008**, *47*, 1485–1487. (c) Kim, J.; Ashenhurst, J. A.; Movassaghi, M. Total Synthesis of (+)-11,11'-Dideoxyverticillin A. *Science* **2009**, *324*, 238–241. (d) Movassaghi, M.; Ahmad, O. K.; Lathrop, S. P. Directed Heterodimerization: Stereocontrolled Assembly via Solvent-Caged Unsymmetrical Diazene Fragmentation. *J. Am. Chem. Soc.* **2011**, *133*, 13002–13005. (e) Lathrop, S. P.; Movassaghi, M. Application of Diazene-Directed Fragment Assembly to the Total Synthesis and Stereochemical Assignment of (+)-Desmethyl-*meso*-Chimonanthine and Related Heterodimeric Alkaloids. *Chem. Sci.* **2014**, *5*, 333–340. (f) Linovska, P.; Movassaghi, M. Concise Synthesis of (–)-Hodgkinsine, (–)-Calycosidine, (–)-Hodgkinsine B, (–)-Quadrigemine C, and (–)-Psycholeine via Convergent and Directed Modular Assembly of Cyclotryptamines. *J. Am. Chem. Soc.* **2017**, *139*, 17590–17596.

[13] For select syntheses of calycanthine and chimonanthine, see: (a) Hendrickson, J. B.; Göschke, R.; Rees, R. Total Synthesis of the Calycanthous Alkaloids. *Tetrahedron* **1964**, *20*, 656–579. (b) Snell, R. H.; Woodward, R. L.; Willis, M. C. Catalytic Enantioselective Total Synthesis of Hodgkinsine B. *Angew. Chem., Int. Ed.* **2011**, *50*, 9116–9119. (c) Mitsunuma, H.; Shibasaki, M.; Kanai, M.; Matsunaga, S. Catalytic Asymmetric Total Synthesis of Chimonanthine, Folicanthine, and Calycanthine Through Double Michael Reaction of Bisoxindole. *Angew. Chem., Int. Ed.* **2012**, *51*, 5217–5221. (d) Trost, B. M.; Osipov, M. Palladium-Catalyzed Asymmetric Construction of Vicinal All-Carbon Quaternary Stereocenters and Its Application to the Synthesis of Cyclotryptamine Alkaloids. *Angew. Chem., Int. Ed.* **2013**, *52*, 9176–9181. (e) Ding, M.; Liang, K.; Pan, R.; Zhang, H.; Xia, C. Total Synthesis of (+)-Chimonanthine, (+)-Folicanthine, and (–)-Calycanthine. *J. Org. Chem.* **2015**, *80*, 10309–10316. (f) Babu, K. N.; Roy, A.; Singh, M.; Bisai, A. Thiourea-Catalyzed Enantioselective Malonate Addition onto 3-Sulfonyl-3'-Indolyl-2-Oxindoles: Formal Total Synthesis of (–)-Chimonanthine, (–)-Folicanthine, and (+)-Calycanthine. *Org. Lett.* **2018**, *20*, 6327–6331. (g) Gentry, E. C.; Rono, L. J.; Hale, M. E.; Matsura, R.; Knowles, R. R. Enantioselective Synthesis of Pyrroloindolines via Noncovalent Stabilization of Indole Radical Cations and Applications to the Synthesis of Alkaloid Natural Products. J. Am. Chem. Soc. 2018, 140, 3394–3402. (h) Kumar, N.; Das, M. K.; Ghosh, S.; Bisai, A. Development of Catalytic Deacylative Alkylations (DaA) of 3-acyl-2-oxindoles: Total Synthesis of meso-Chimonanthine and Related alkaloids. *Chem. Commun.* **2017**, *53*, 2170–2173.

[14] A common related approach involves pre-formation of oxindoles instead of indoline ring systems; see ref 2.

[15] (a) Dotson, J. J.; Perez-Estrada, S.; Garcia-Garibay, M. A. Taming Radical Pairs in Nanocrystalline Ketones: Photochemical Synthesis of Compounds with Vicinal Stereogenic All-Carbon Quaternary Centers. *J. Am. Chem. Soc.* **2018**, *140*, 8359–8371. (b) Natarajan, A.; Ng, D.; Yang, Z.; Garcia-Garibay, M. A. Parallel Synthesis of (+)- and (–)-α-Cuparenone by Radical Combination in Crystalline Solids. *Angew. Chem., Int. Ed.* **2007**, *46*, 6485–6487.

[16] For select examples of solid-state photodecarbonylation reactions with retention of stereochemistry, see: (a) Hérnandez-Linares, M. G. H.; Guerrero-Luna, G.; Pérez-Estrada, S.; Ellison, M.; Ortin, M.-M.; Garcia-Garibay, M. A. Large-Scale Green Chemical Synthesis of Adjacent Quaternary Chiral Centers by Continuous Flow Photodecarbonylation of Aqueous Suspensions of Nanocrystalline Ketones. *J. Am. Chem. Soc.* **2015**, *137*, 1679–1684. (b) Resendiz, M. J. E.; Natarajan, A.; Garcia-Garibay, M. A. Diastereoselective Synthesis and Spin-Dependent Photodecarbonylation of Di(3-Phenyl-2-Pyrrolidinon-3-yl)Ketones: Synthesis of Nonadjacent and Adjacent Stereogenic Quaternary Centers. *Chem. Commun.* **2008**, 193–195. (c) Resendiz, M. J. E.; Family, F.; Fuller, K.; Campos, L. M.; Khan, S. I.; Lebedeva, N. V.; Forbes, M. D. E.; Garcia-Garibay, M. A. Radical Reactions with Double Memory of Chirality (^{2}MOC) for the Enantiospecific Synthesis of Adjacent Stereogenic Quaternary Centers in Solution: Cleavage and Bonding Faster Than Radical Rotation. *J. Am. Chem. Soc.* **2009**, *131*, 8425–8433. (d) Resendiz, M. Photochemical Decarbonylation of Ketones in the Solid State and in Solution. Progress Towards The Synthesis Of Natural Products, Ph. D. Thesis, UCLA, 2008.

[17] Although a non-brominated analog of **9** has been shown to undergo solid-state photodecarbonylation (see reference 16b), we have found that the presence of certain ortho-substituents on the aromatic rings is problematic for the photodecarbonylation reaction.

[18] An alternative strategy was explored involving the use of phosgene and two equivalents of an enolate species. However, this protocol was found to be unsuccessful. For the parent transformation being carried out on a non-brominated starting material, see references 16b,c.

[19] X-ray structures were rendered using CYLview; see: Legault, C.Y. *CYLview*, 1.0b; Université de Sherbrooke: Quebec, 2009; http://www.cylview.org.

[20] To our knowledge, this is the first documented case of disproportionation in a crystalline solid-state photodecarbonylation reaction. An explanation for this reactivity is currently under investigation and will be reported in due course.

[21] Although we cannot rule out the formation of the corresponding *meso* isomer of **21** to a minor extent, we estimate the selectivity to be >9:1.

[22] (a) Yang, Z.; Ng, D.; Garcia-Garibay, M. A. Engineering Reactions in Crystalline Solids: Photochemical Generation of Secondary and Tertiary Enol Radical Pairs from Crystalline Ketodiesters. *J. Org. Chem.* **2001**, *66*, 4468–4475. (b) Campos, L. M.; Dang, H.; Ng, D.;

Yang Z.; Martinez, H. L.; Garcia-Garibay, M. A. Engineering Reactions in Crystalline Solids: Predicting Photochemical Decarbonylation from Calculated Thermochemical Parameters. *J. Org. Chem.* **2002**, *67*, 3749–3754. (c) Ng, D.; Yang, Z.; Garcia-Garibay, M. A. Engineering Reactions in Crystals; *gem*-Dialkoxy Substitution Enables the Photodecarbonylation of Crystalline 2-Indanone. *Tetrahedron Lett.* **2002**, *43*, 7063–7066.

[23] Zhu, W.; Ma, D. Synthesis of Aryl Azides and Vinyl Azides *via* Proline-Promoted CuI-Catalyzed Coupling Reactions. *Chem. Commun.* **2004**, 888–889.

[24] Optimization efforts for this step were regrettably cut short because of COVID-19 related laboratory shutdowns, although preliminary optimization studies showed that the double azidation step could be achieved in 51% yield (according to ^{1}H NMR analysis with an external standard, average of two experiments).

[25] Although the two-step yield from **7** to **25** proceeds with a 78% loss of mass balance, we surmise that most of this (>65%) occurred during the cross-coupling step (based on ^{1}H NMR analysis of crude **22**). Therefore, if isomeric products resulted from the reduction of **22** they were present in <18% yield.

[26] "Dihydropsychotriadine" (**25**) has not yet been found in nature. Whether or not this compound is naturally-occurring remains an open question.

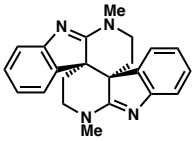
[27] Presumed intermediate **24** could plausibly undergo cyclization to form either a 6-membered ring (observed) or a 5-membered ring. It is surprising that the latter was not observed as related reductive cyclizations have been reported to form the 5-membered ring under similar conditions (see references 11a–c and 13h). Of note, the studies disclosed in references 11a–c and 13h, which include alkyl substituents on the oxindole nitrogens, presumably undergo reduction of the oxindole to aldehyde oxidation state followed by a reversible, thermodynamically controlled cyclization to form a 5-membered ring. We speculate that the system disclosed herein may undergo a kinetically controlled cyclocondensation of the amine onto the oxindole to form a 6-membered ring.

[28] Other possible mechanisms exist for the conversion of **22** to **25** that do not involve formation of bis(oxindole) **24**; see Scheme S5 in the Supporting Information.

[29] Oxidation conditions adapted from: Higuchi, K.; Sato, Y.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. First Total Synthesis of Hinckdentine A. *Org. Lett.* **2009**, *11*, 197–199.

[30] Calculations suggest that **28** is 8.7 kcal/mol higher in energy than **27** (ωB97XD/6-31G(d,p)). As such, it is unlikely that **27** spontaneously rearranges to **28** during isolation. It is plausible that the substrate in a lower oxidation state, "tetrahydropsychotriadine," could readily isomerize to give calycanthine or chimonanthine. Related scaffolds reminiscent of "tetrahydropsychotriadine" have only been isolated previously when constrained due to the presence of additional ring systems (see references 9 and 10). Preliminary efforts aimed at reducing **25** to the corresponding geminal diamine were either met with decomposition or led to recovered starting material (see Figure S4 in the Supporting Information).

SYNOPSIS TOC



"Psychotriadine"

- *Piperidinoindoline skeletal isomer of bis(cyclotryptamine) alkaloids*
- *Accessed via chemical synthesis using a solid-state photodecarbonylation strategy*
- *Found upon re-analysis of Psychotria colorata flower extracts*