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

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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 have a rich history.[2a,b] For example, although calycanthine was isolated in 1888, its structure

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Supporting Information

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Detailed experimental procedures and compound characterization data (PDF)

Crystallographic data for **18** (CIF)

Crystallographic data for **9** (CIF)

Crystallographic data for **19** (CIF)

Crystallographic data for **25** (CIF)

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remained a mystery until 1954, when Robinson and 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 a constitutional isomer of 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 co-workers 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 group 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 because of 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 preformed indoline (or related) ring systems.[14] In this Communication, 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.

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**. Because of conformational restrictions imposed by the rigid reaction cavity of the crystal lattice, as 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.[15–17] Moreover, this key step would complement the elegant radical-based approach for accessing cyclotryptamine alkaloids pioneered by Movassaghi and co-workers.[12] Ketone **9** would be prepared from acid chloride **10** and enolate **11**.[18]

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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 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 on the basis of 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 nonspecific 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.

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 *p*-methoxybenzyl (PMB) protecting groups (Figure 2A; see the Supporting Information 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]

The dramatically different reactivities of ketones **18** and **19** can be rationalized by the analysis shown in Figure 2C and inspection of the single-crystal X-ray structures (see Figure 2B)[19] for the two compounds. Solid-state photodecarbonylation requires stabilization of the breaking C–C σ-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 σ 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, when the dihedral angle is 0°, the C–C σ-bond and π-system are orthogonal, resulting in no electronic stabilization. In considering ketone **18**,

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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 because of 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 single 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 ^1H NMR analysis. However, the formation of other isomeric products cannot be ruled out at this time.

Prior to unambiguously establishing the structure of **25** by X-ray diffraction, we had surmised that **25** could be an aminal stereoisomer of **26**. Therefore, **25** was treated under Ley–Griffith oxidation conditions to ablate the aminal stereocenter.[29] The product, which we obtained in 74% yield, was compared to an authentic sample of dehydrobhesine (**27**) obtained from extracts from *P. 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 the 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 *P. 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. Reanalysis of *P. colorata* flower extracts revealed the presence of "psychotriadine", suggesting that it is likely a naturally occurring alkaloid. These studies not only underscore the value of solid-state photodecarbonylation chemistry in total

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synthesis but also demonstrate that all five of the distinct bis(cyclotryptamine) alkaloid frameworks originally proposed are represented in nature.

Supplementary Material

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(17). Although a non-brominated analogue of **9** has been shown to undergo solid-state photodecarbonylation (see ref 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 2 equiv 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 refs 16b,c.

(19). X-ray structures were rendered using CYLview. See:Legault CY *CYLview*, ver. 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.

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(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

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crude **22**). Therefore, if isomeric products resulted from the reduction of **22** they were present in < 13% yield.

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

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

(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. [PubMed: 19055376]

(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 by the presence of additional ring systems (see refs 9 and 10). Preliminary efforts aimed at reducing **25** to the corresponding geminal diamine either were met with decomposition or led to recovered starting material (see Figure S4).

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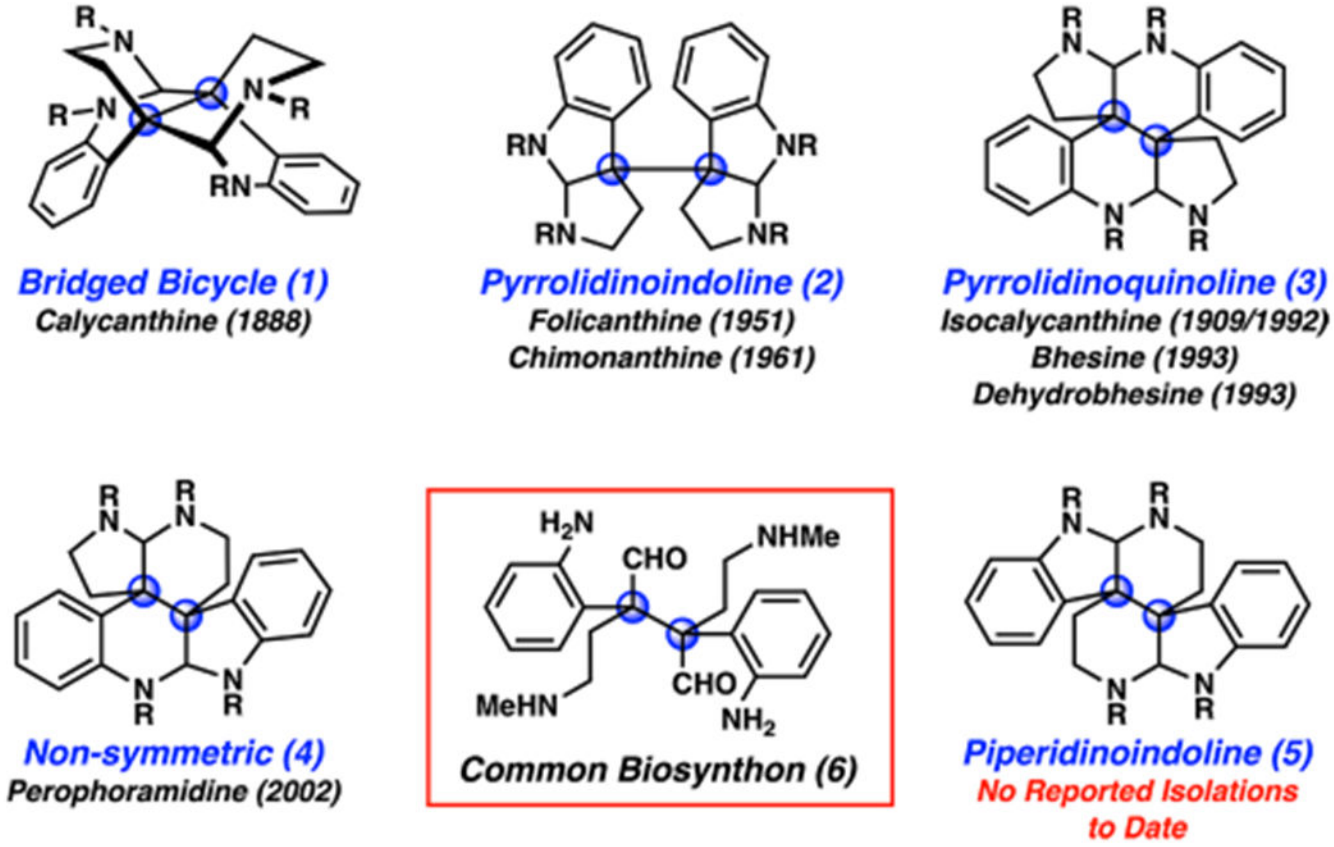

Figure 1.

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

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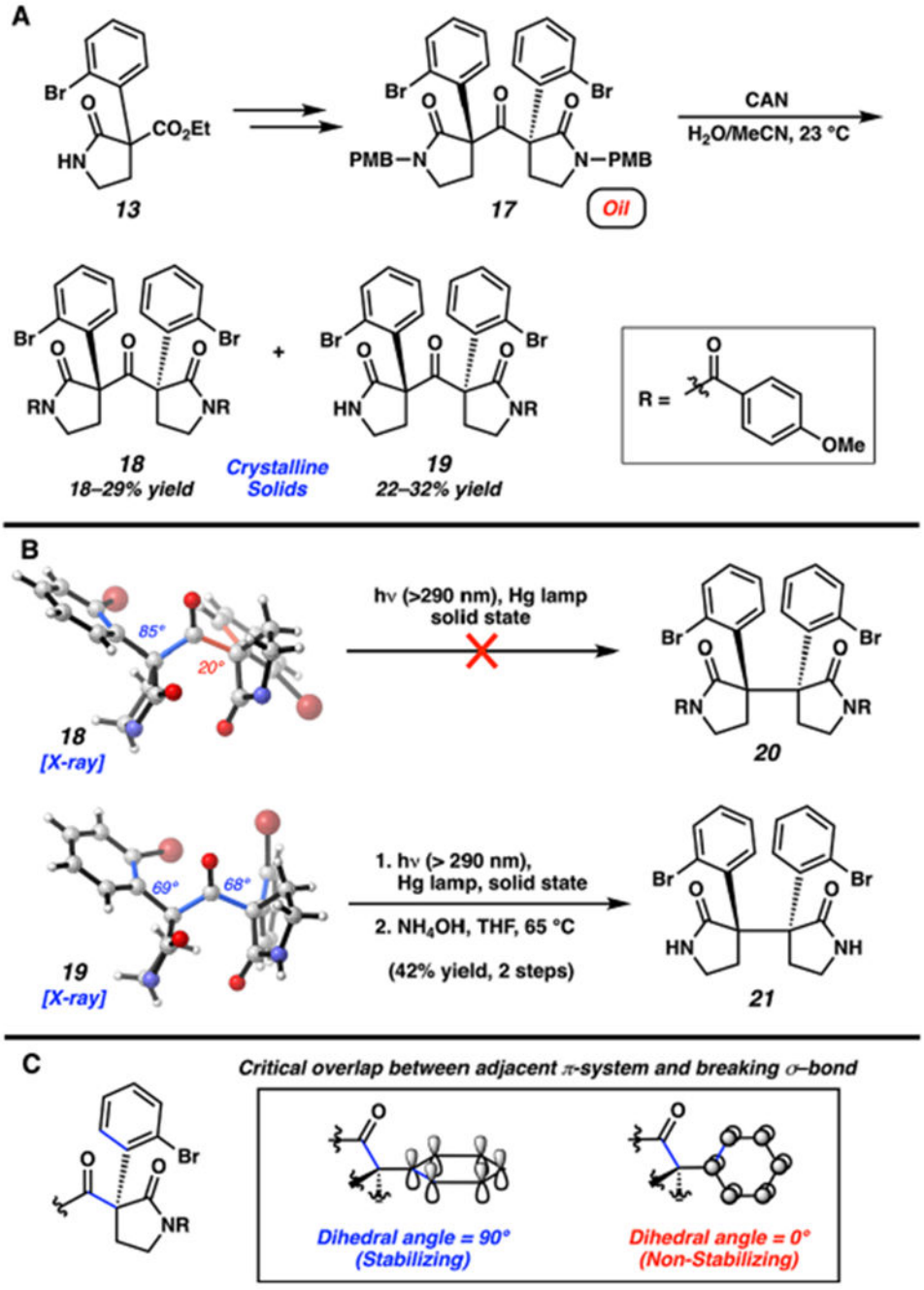

Figure 2.

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

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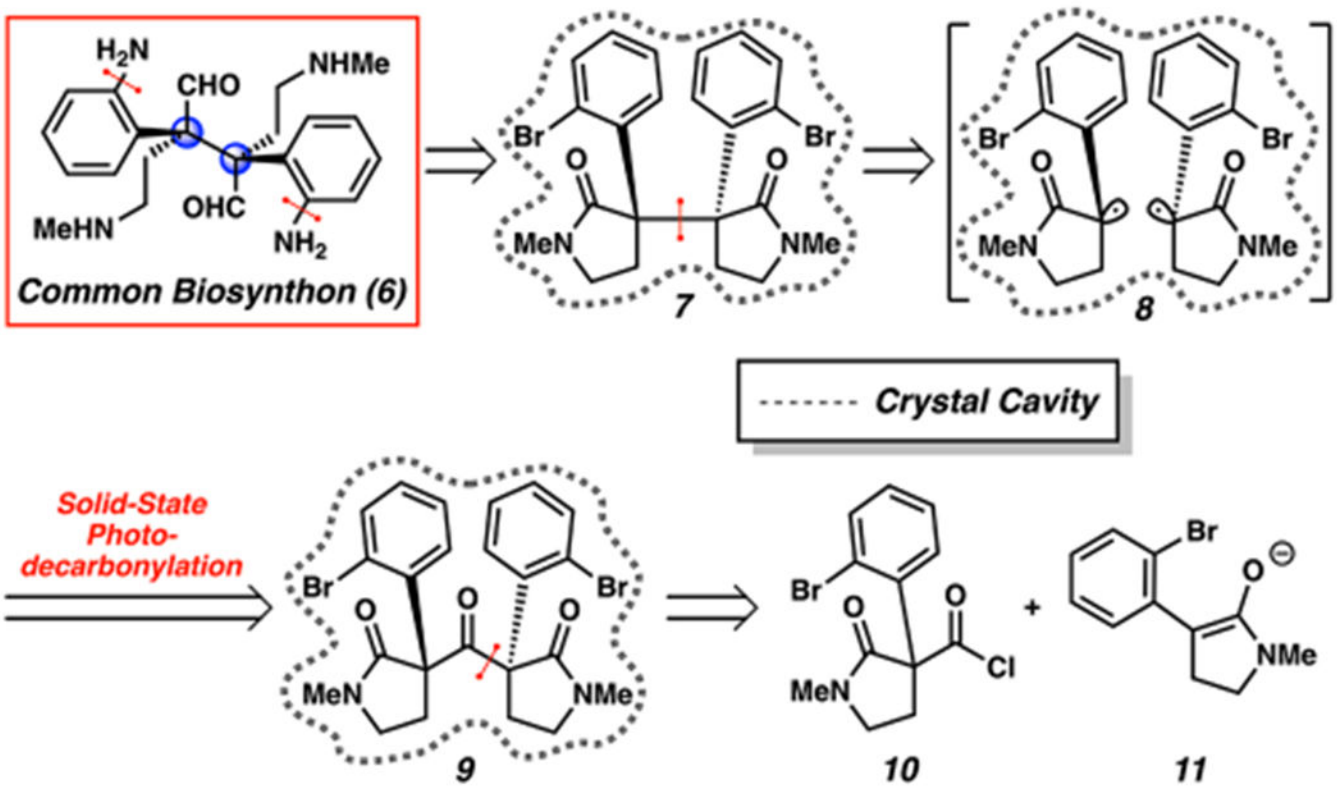

Scheme 1.

Retrosynthetic Analysis of Biosynthon 6 with Key Stereospecific Radical Combination in the Crystalline State

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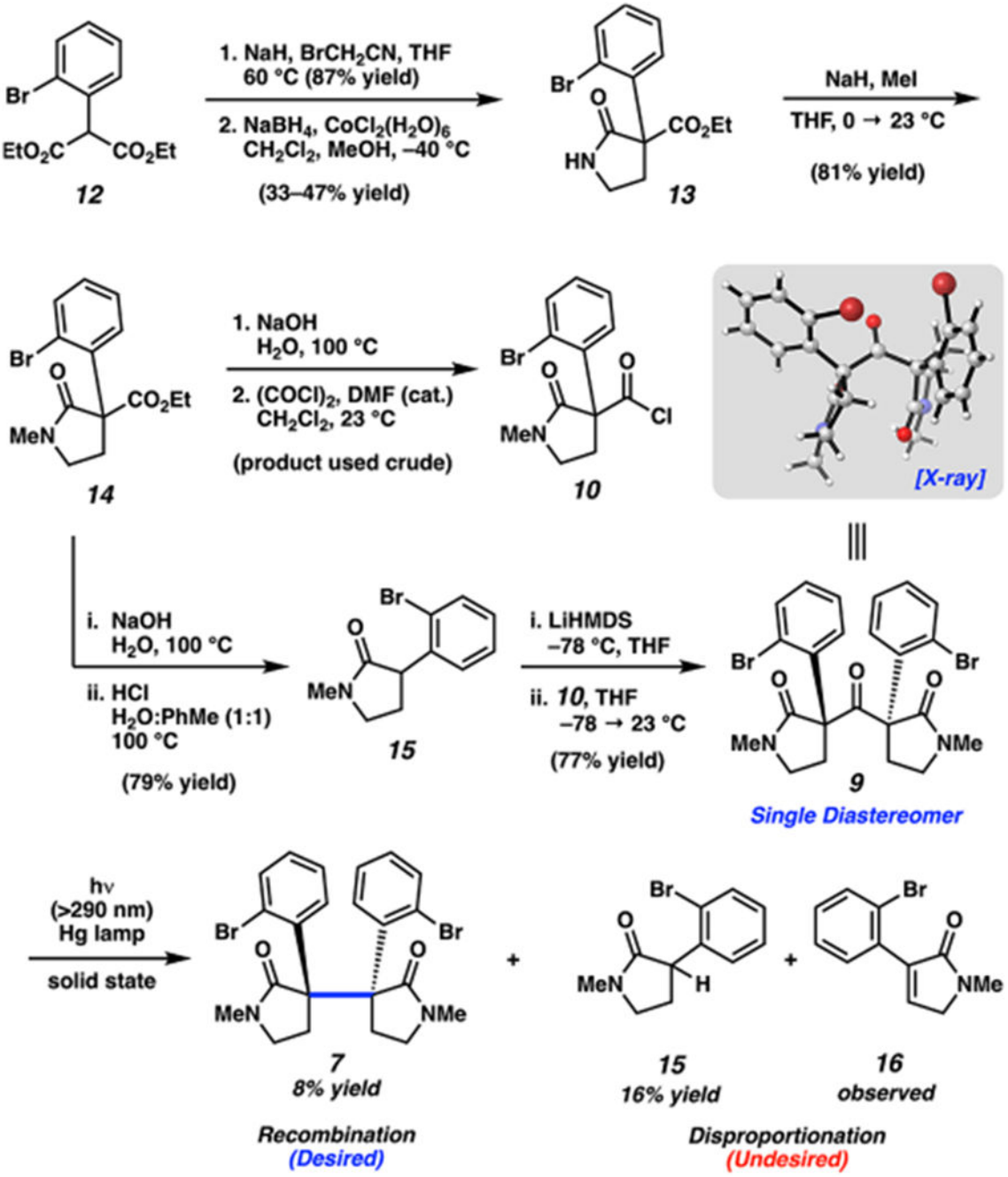

Scheme 2.
Synthesis and Photodecarbonylation of Ketone 9

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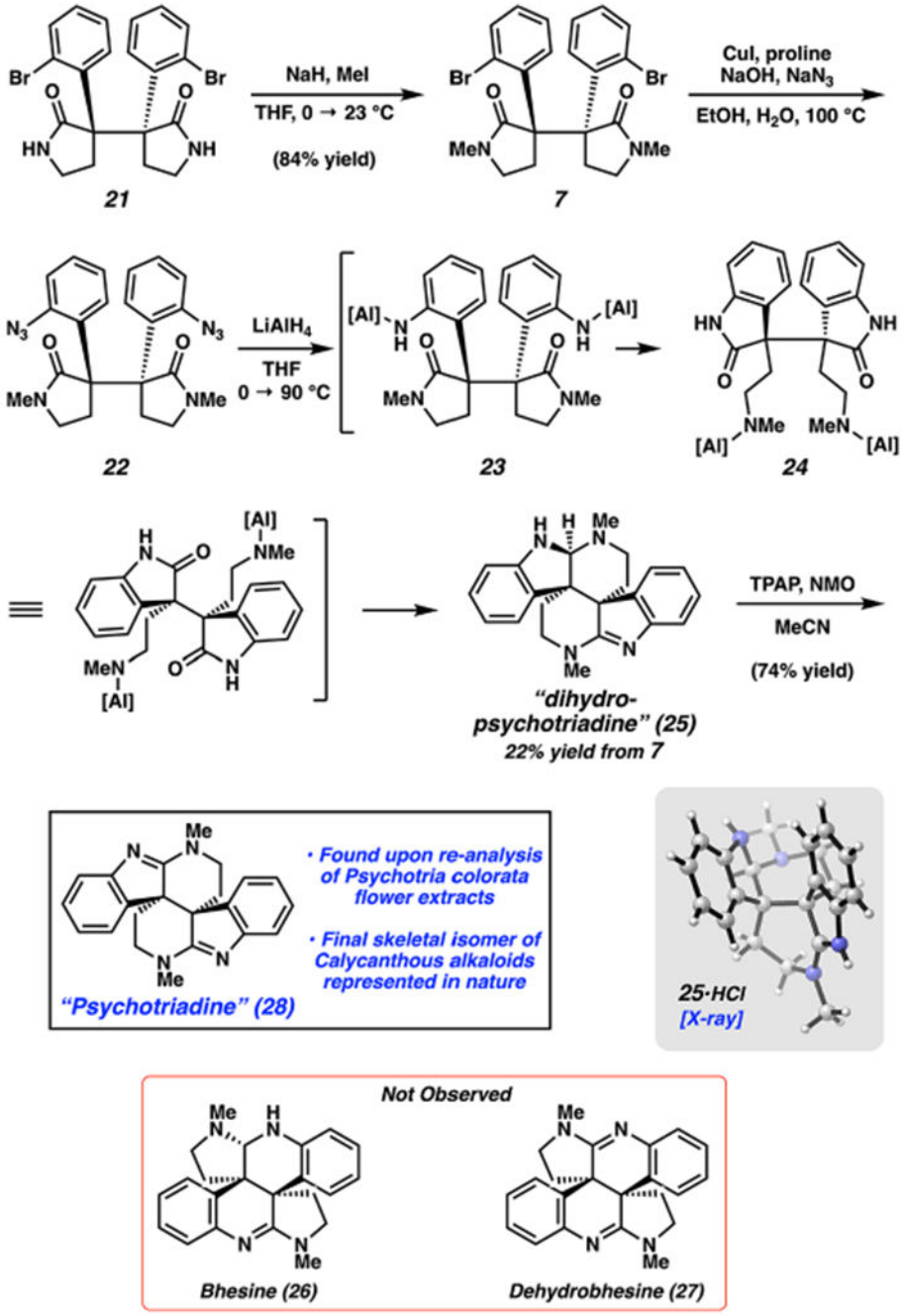

Scheme 3.

Total Synthesis of "Psychotriadine" (28) Bearing the Piperidinoindoline Scaffold (the Chloride Counterion of the X-ray Structure of 25 Has Been Omitted for Clarity)