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# Synthesis of (+)-Lysergol and Its Analogues To Assess Serotonin Receptor Activity

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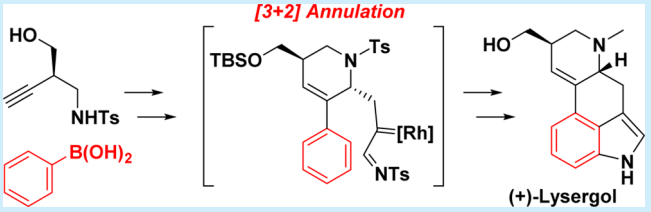
Supporting Information

**ABSTRACT:** An efficient synthesis of ergot alkaloid lysergol and its analogues is described, providing compounds for functional evaluation at the human 5-$HT_{1A}$, 5-$HT_{2A}$, 5-$HT_{2B}$, or 5-$HT_{2C}$ receptors. Key features of the synthesis include the development of a tandem reaction to construct the multifunctionalized piperidine skeleton and use of a rhodium-catalyzed [3 + 2] annulation in the late-stage indole formation.




The total synthesis of small-molecule natural products provides a reliable method for making deep-seated and flexible structural changes of a targeted chemotype, leading to valuable analogues that are inaccessible from semisynthesis or synthetic biology.[1] We have therefore embarked on a synthetic program to assemble a collection of natural products and their analogues for biological evaluation, which ensures the reproducible and comparable data.[2] Lysergol (**1**) and lysergic acid (**2**) are prototypes of ergot alkaloids that have important pharmacological properties[3] that engage various serotonin G protein-coupled receptors (Figure 1).[4] Among the serotonin (5-HT) receptors, 5-$HT_{1A}$ and 5-$HT_2$ have been the most studied due to their involvement in emotional, neuropsychiatric, and neurodegenerative disorders.[5] For instance, agonists against 5-$HT_{1A}$ have been heralded as a new class of antidepressant drugs,[6] while 5-$HT_{2A}$ agonists have the potential for enhancing cognition.[7] Herein, we describe a new synthesis of (+)-lysergol (**1**) in a concise and enantioselective manner that will facilitate the study of structure−activity relationships.

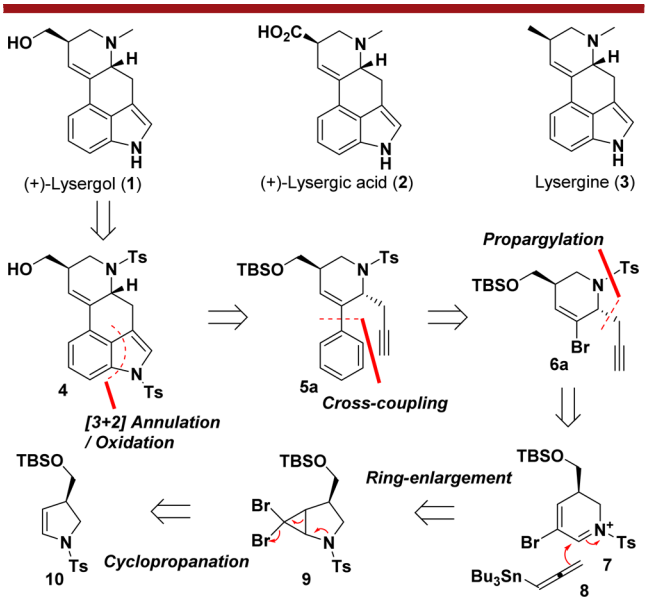



**Figure 1.** Retrosynthetic analysis of (+)-lysergol (**1**).

Even though the chemical synthesis of the ergot alkaloids has been intensively investigated over the last six decades, most approaches either used substituted indoles as the starting materials or constructed the indole ring in the early stage of the synthesis.[8] In a previous report, we delineated the synthesis of lysergine (**3**) via a radical cyclization/fragmentation strategy, also starting from an indole fragment.[9] In order to prepare ergot alkaloid analogues with substituents on the phenyl ring to optimize their affinity and selectivity at 5-HT receptor subtypes,[10] we investigated the potential of forging the indole ring at a late stage in the synthesis. An intramolecular dearomatizing [3 + 2] annulation reaction to furnish 3,4-fused indole skeletons developed by Murakami and co-workers attracted our attention, which has been used for the synthesis of racemic Uhle's ketone, a precursor for ergot alkaloids.[11] We envisaged that this reaction could be used to construct **4**, a late-stage intermediate for the synthesis of (+)-lysergol (**1**), if a highly substituted tetrahydropyridine (**5a**) could be readily prepared (Figure 1). Moreover, introduction of the phenyl group to the highly substituted tetrahydropyridine **5a** by Pd-catalyzed cross-coupling with bromide **6a** would allow easy variation of the substituents on the phenyl ring for analogue generation. We proposed that the ring-opening of *gem*-dibromocyclopropane **9** would give rise to iminium **7**,[12] which could be trapped in situ by allenyltributyltin **8** to produce **6a**. Intermediate **9** could in turn be prepared through cyclopropanation of the simple monocyclic enamine **10**.

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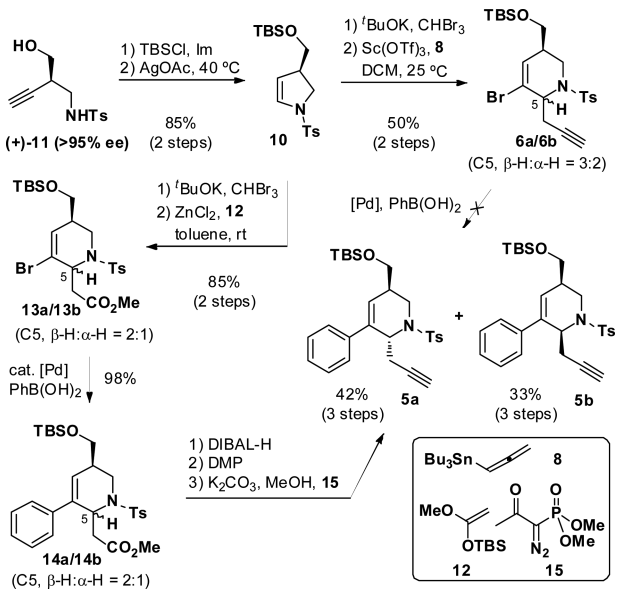
We commenced our studies by making chiral alcohol **11** from (*R*)-Garner's aldehyde following the reported procedures, which took five steps with 48% overall yield (Scheme 1).[8p]

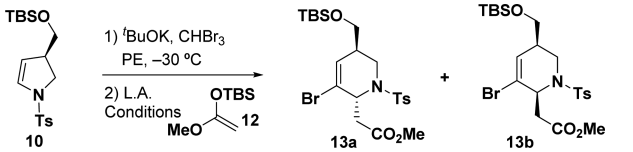
**Scheme 1. Synthesis of 5a and 5b**




Protecting the primary alcohol of **11** with TBS followed by silver-catalyzed 5-*endo-dig* cyclization afforded **10** in 85% yield over two steps.[13] The reaction of **10** with dibromocarbene proceeded smoothly in petroleum ether at −30 °C,[14] but the product was not stable and was therefore subjected to the propargylation reaction without flash chromatography. This procedure eventually gave rise to a pair of inseparable diastereomers **6a** and **6b** (ratio 3:2) using 1.1 equiv of $Sc(OTf)_3$ and 3 equiv of allenyltributyltin **8** in the second step. Unfortunately, a variety of Pd-catalyzed coupling reactions, including Suzuki, Stille, and Negishi reactions, failed to provide the desired tetrahydropyridines (**5a**/**5b**). The presence of a neighboring alkyne to the alkenyl bromide may have caused complications as the 4-*exo-dig* cyclocarbopalladation has been well-documented for this structure feature.[15]

To overcome this synthetic hurdle, we switched to silyl ketene acetal **12** as the nucleophile and further optimized the conditions to furnish **13a** and **13b** (Table 1). Interestingly, only a trace amount of product was obtained when $Sc(OTf)_3$ was used as the Lewis acid (entry 1). When the ring-enlargement/nucleophilic addition reaction was promoted by 1.1 equiv of AgOTf, **13a** and **13b** were obtained in 50% overall yield with a 2:1 ratio (entry 2). Even though 1.1 equiv of $ZnCl_2$ gave a low yield (38%, entry 3), reducing the amount of Lewis acid to 0.1 equiv significantly improved the reaction efficiency (60%, entry 4), indicating the decomposition of **12** in the presence of the Lewis acid could be an issue in this cascade transformation. We were delighted to find that increasing the amount of C-nucleophile **12** afforded **13a** and **13b** in 83% overall yield with a 5:3 ratio (entry 5). However, lowering the reaction temperature to 0 °C essentially shut down the reaction (entry 6). Several solvents were also examined (entries 7−9), revealing that toluene behaved slightly better than THF (entry 9). The preference for 1,2-addition over 1,4-addition is consistent with the observation made by Rutjes and co-workers for the reaction

**Table 1. Optimization of the Ring-Opening/Nucleophilic Substitution Cascade Reaction**



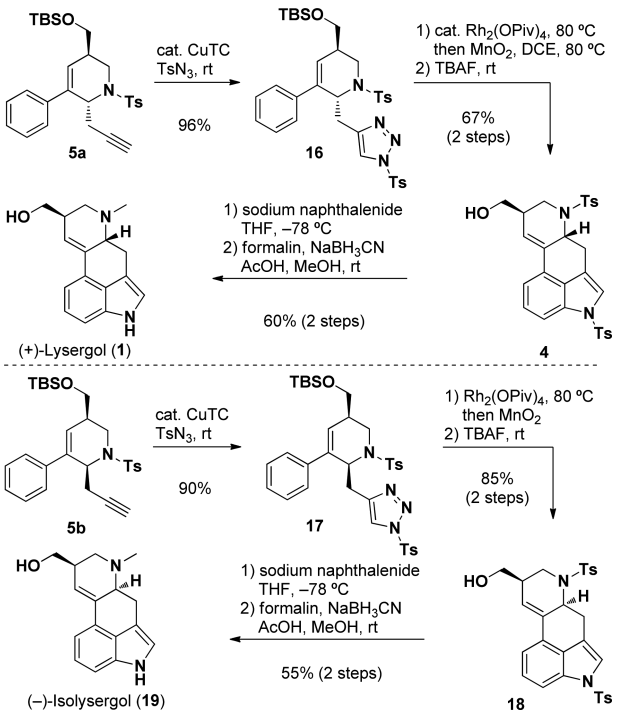

| entry | Lewis acid (equiv) | conditions[a] | time (h) | yield (%) (13a/13b)[b] |
|---|---|---|---|---|
| 1 | $Sc(OTf)_3$ (1.1) | THF, rt | 1 | trace[c] |
| 2 | AgOTf (1.1) | THF, rt | 1 | 50 (2:1)[c] |
| 3 | $ZnCl_2$ (1.1) | THF, rt | 1 | 38 (5:3)[c] |
| 4 | $ZnCl_2$ (0.1) | THF, rt | 2 | 60 (5:3)[c] |
| 5 | $ZnCl_2$ (0.1) | THF, rt | 2 | 83 (5:3)[d] |
| 6 | $ZnCl_2$ (0.1) | THF, 0 °C | 5 | 7 (5:3)[d] |
| 7 | $ZnCl_2$ (0.1) | MeCN, rt | 1.5 | 53 (3:1)[d] |
| 8 | $ZnCl_2$ (0.1) | DCM, rt | 2 | 65 (2:1)[d] |
| 9 | $ZnCl_2$ (0.1) | toluene, rt | 3 | 85 (2:1)[d] |

[a]The reaction was carried out with 0.15 mmol of **10**; 1.5 mL of solvent was used in the second step. [b]Isolated yield after flash chromatography. [c]1.3 equiv of **12** was used. [d]2.0 equiv of **12** was used.

of a similar *N*-sulfonyliminium intermediate with carbon-based nucleophiles.[16]

The mixture of **13a** and **13b** underwent Suzuki coupling with phenylboronic acid to provide **14a** and **14b** in excellent yield. Fortunately, after the redox manipulation and Seyferth−Gilbert homologation using Bestmann−Ohira reagent **15**, a pair of C5 epimers, alkynes **5a** and **5b**, could be readily separated by flash chromatography. After the stereochemistry of **5a** and **5b** was assigned by extensive 2D-NMR experiments (see the Supporting Information), the next step was to convert them to lysergol (**1**) and isolysergol (**19**), respectively (Scheme 2). To this end, *N*-sulfonyl-1,2,3-triazole **16** was first prepared

**Scheme 2. Synthesis of (+)-Lysergol (1) and (−)-Isolysergol (19)**



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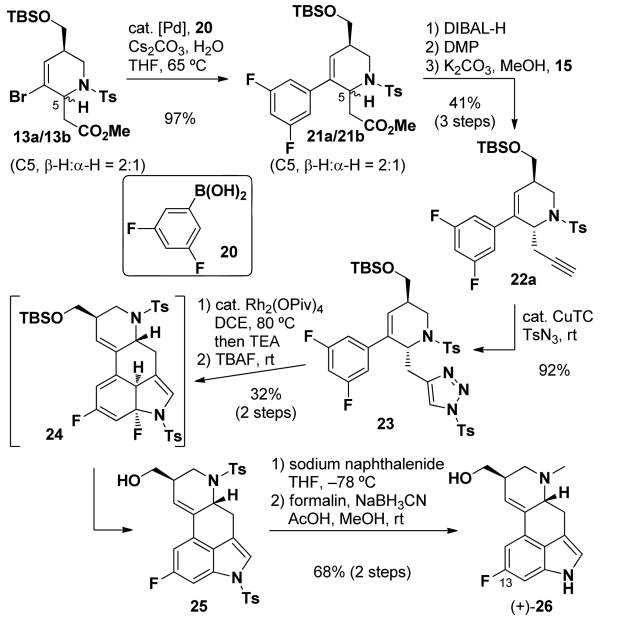
using a copper-catalyzed [3 + 2] cycloaddition. A subsequent rhodium-catalyzed intramolecular dearomatizing [3 + 2] annulation reaction followed by oxidative aromatization and deprotection of the TBS group furnished compound **4** in 67% yield over two steps. Eventually, deprotection of Ts groups and reductive amination completed the total synthesis of (+)-lysergol (**1**). In parallel, subjecting **5b** to the same sequence of transformations afforded (−)-isolysergol (**19**). Interestingly, the [3 + 2] annulation/rearomatization tandem reaction gave a better yield of the corresponding indole product (**18**) in this scenario. It is noteworthy that both enantiomers of **4** and **18** have been prepared via an elegant Pd-catalyzed domino reaction by the group of Fujii and Ohno.[8p] The spectroscopic data of the synthesized samples of **1**, **4**, **18**, and **19** were in good agreement with those reported in the literature.[8j,o,p,17]

Encouraged by the synthesis of (+)-lysergol (**1**) and (−)-isolysergol (**19**), we moved on to prepare an analogue of lysergol with the C13 hydrogen substituted by fluorine (**26**, Scheme 3). To this end, 3,5-difluorophenylboronic acid **20** was

**Scheme 3. Synthesis of (+)-13-Fluorolysergol (26)**




used in the Suzuki coupling reaction with bromides **13a** and **13b**. Following the same protocols, tetrahydropyridine **22a** was isolated in 41% yield through the redox manipulations and homologation and was further converted to *N*-sulfonyl-1,2,3-triazole **23** in high yield. In this case, the rhodium-catalyzed intramolecular dearomatizing [3 + 2] annulation reaction was followed by the addition of excess TEA to facilitate the elimination of the hydrogen fluoride of intermediate **24**. The subsequent TBS deprotection provided **25** in 32% yield over two steps. Removal of the Ts groups and reductive amination eventually lead to (+)-**26** in 68% yield over two steps.

The agonist properties of compounds **1**, **3**, **19**, and **26** were evaluated in a calcium flux assay using CHO-K1 cells expressing 5-$HT_{1A}$, 5-$HT_{2A}$, 5-$HT_{2B}$, or 5-$HT_{2C}$ with serotonin as the positive control (Table 2 and Figures S1−4).[18] All four compounds demonstrated full agonism at the 5-$HT_{1A}$ receptor, with (+)-lysergol (**1**) being over 5-fold more potent than the other three. (+)-Lysergol (**1**) also proved to be a partial agonist

**Table 2. Agonist Properties of Lysergol and Analogues at Serotonin Receptors**

| | $EC_{50}$ ± SEM (nM) | | | |
|---|---|---|---|---|
| compd | 5-$HT_{1A}$ | 5-$HT_{2A}$ | 5-$HT_{2B}$ | 5-$HT_{2C}$ |
| 5-HT | 11 ± 2 | 0.96 ± 0.14 | 0.071 ± 0. 010 | 0.14 ± 0.03 |
| (+)-**1** | 73 ± 6 | 1.6 ± 0.5[a] | >10000 | 6.6 ± 1.4[b] |
| (±)-**3** | 342 ± 23 | 2.7 ± 1.6[c] | 145 ± 54[d] | 103 ± 9[e] |
| (−)-**19** | 481 ± 31 | >10000 | >10000 | >10000 |
| (+)-**26** | 424 ± 27 | 12 ± 3[f] | >10000 | >10000 |

[a]51% max 5-HT stimulation. [b]43% max 5-HT stimulation. [c]57% max 5-HT stimulation. [d]36% max 5-HT stimulation. [e]42% max 5-HT stimulation. [f]17% max 5-HT stimulation.

at both 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors with single-digit nanomolar $EC_{50}$. In comparison, (+)-13-fluorolysergol (**26**), substituting a fluoride for the C13 hydrogen of **1**, exhibited substantially lower potency (12 nM vs 1.6 nM) and efficacy (17% vs 51% $E_{max}$) at the 5-$HT_{2A}$ receptor and lost the ability to activate the 5-$HT_{2c}$ receptor. (−)-Isolysergol (**19**), the enantiomer of (+)-isolysergol synthesized previously,[8o,p,17] only activated the 5-$HT_{1A}$ receptor, implying the importance of the C5 stereogenic center in (+)-lysergol (**1**). Even though further investigation is required, the preliminary data for racemic lysergine (**3**) suggest that the hydroxyl group in (+)-lysergol (**1**) plays a role in interacting with the 5-HT receptors.

In summary, we have achieved the synthesis of (+)-lysergol (**1**) in 13 steps and 11% overall yield starting from enantiopure **11**. More importantly, the dramatically different properties resulting from a single atom change to lysergol reinforces the value of total synthesis in studying the biological activities of natural products. Our strategy of preparing highly functionalized piperidines and substituted indoles could be further applied to the synthesis of various alkaloids, which is ongoing in our group and will be reported in due course.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03779.

Detailed experimental procedures, compound characterization data, and biological assay protocols (PDF)

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### Notes

The authors declare no competing financial interest.

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