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SYNTHETIC STUDIES TOWARD (+)-LYSERGIC ACID: CONSTRUCTION OF THE TETRACYCLIC ERGOLINE SKELETON

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Abstract – We have successfully constructed the tetracyclic skeleton of lysergic acid, which features an acylation at the C3 position of the indole as well as an intramolecular Heck reaction. The optically active D ring unit could be derived from L-pyroglutamic acid *via* a disrotatory electrocyclic reaction of a dibromocyclopropane.

INTRODUCTION

Ergot alkaloids are biosynthesized by coupling of a variety of amine moieties with a common carboxylic acid, lysergic acid (**1**).¹ Lysergic acid has attracted a lot of attention because of its unique tetracyclic structure as well as the interesting biological activities of ergot alkaloids. While numerous synthetic studies and total syntheses of racemic lysergic acid have been reported to date,² the first total synthesis of (+)-lysergic acid was reported in 2004 by Szántay and coworkers, which involves resolution of a racemic tetracyclic intermediate using (–)-dibenzoyl-L-tartaric acid.³ We have recently achieved the total synthesis of (+)-lysergic acid methyl ester, featuring an enzymatic desymmetrization of a 1,3-diol, an addition of 2,6-dibromophenyllithium to a nitroalkene, and most notably a palladium-mediated double cyclization.⁴ While we were successful in the asymmetric synthesis of (+)-lysergic acid methyl ester, we were not particularly satisfied with the long synthetic route consisting of more than 30 steps. Herein, we report our

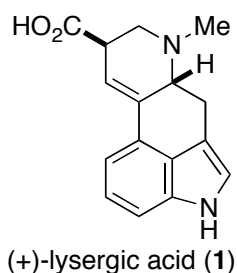
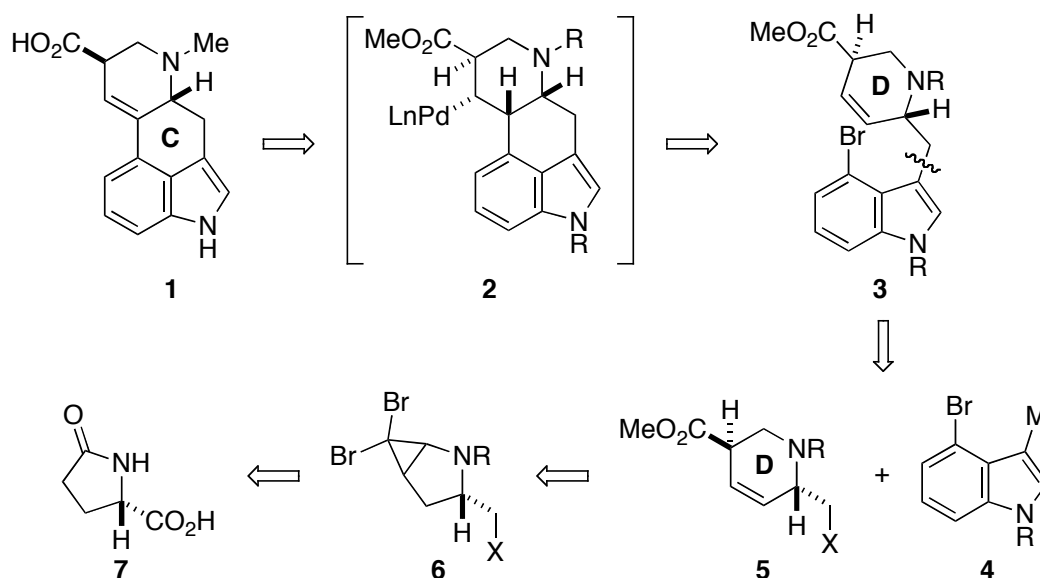


Figure 1. Structure of (+)-lysergic acid.

more recent studies toward the total synthesis of (+)-lysergic acid.

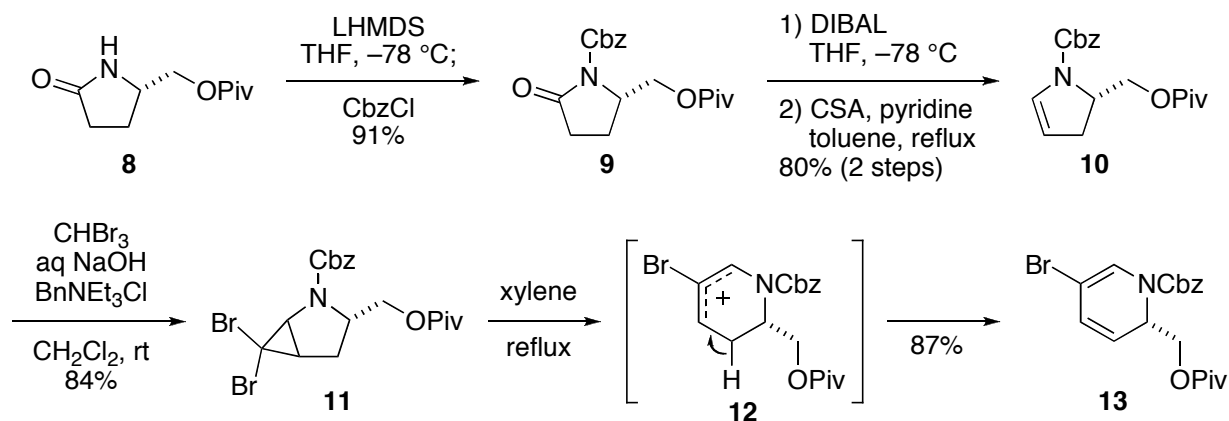
RESULTS AND DISCUSSION

As shown in the retrosynthesis outlined in Scheme 1, the C ring of **1** could be constructed by means of an intramolecular Heck reaction. For smooth β -H elimination, the D ring should be prepared as a *trans*-2,5-disubstituted 1,2,5,6-tetrahydropyridine. Disconnection of **3** at the 3-position of the indole could lead to indole unit **4** and D-ring unit **5**. We envisaged that the tetrahydropyridine moiety of D-ring unit **5** could be derived from L-pyrroglutamic acid (**7**) using an electrocyclic reaction of dibromocyclopropane **6**.⁵



Scheme 1

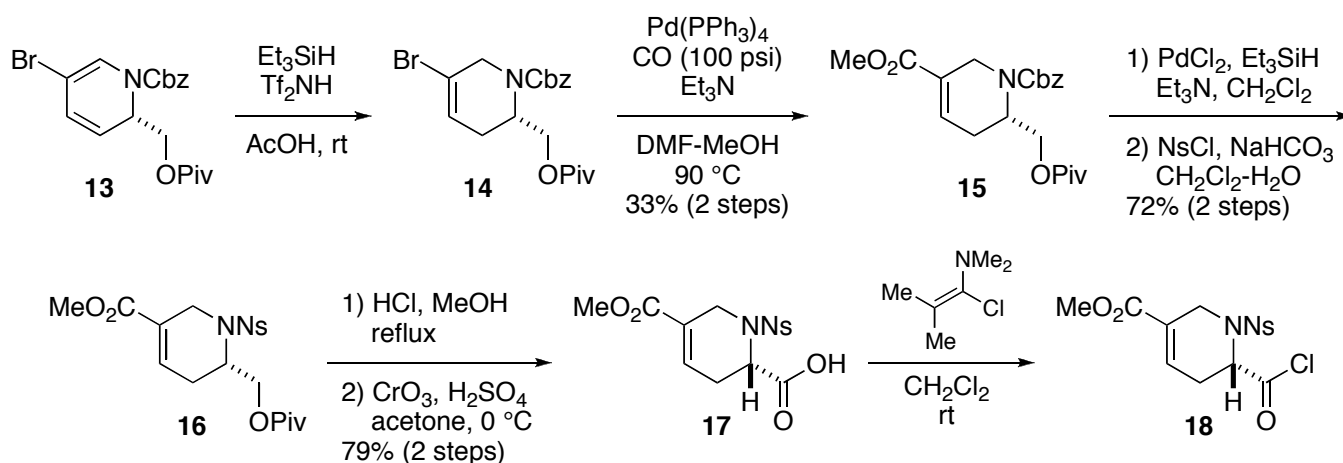
Our synthesis commenced with the acylation of the known lactam **8**, which was derived from L-glutamic acid (Scheme 2).⁶ Thus, successive treatment of **8** with LHMDS and CbzCl gave **9** in good yield. Reduction of **9** with DIBAL and subsequent dehydration of the resulting hemiaminal under slightly acidic conditions afforded enamide **10**. Dibromocyclopropanation of the enamide proceeded smoothly under



Scheme 2

biphasic conditions in the presence of a phase-transfer catalyst to furnish dibromocyclopropane **11**, which, upon heating in refluxing xylene, underwent a disrotatory electrocyclic reaction to give directly the optically active dihydropyridine **13** as a result of the spontaneous deprotonation of the cation **12**.

Dihydropyridine **13** was transformed into D-ring unit **18** by way of a seven-step sequence (Scheme 3). Thus, reduction of **13** with triethylsilane under acidic conditions occurred regioselectively to give **14**, which was then subjected to carbonylation with a palladium catalyst to afford ester **15**. Removal of the Cbz group in the presence of a double bond was achieved using Ritter's method,⁷ and subsequent nosylation of the resulting secondary amine furnished **16**. Acidic cleavage of the pivalate ester followed by Jones oxidation gave carboxylic acid **17**,⁸ which was converted into acid chloride **18** according to Ghosez's procedure.⁹

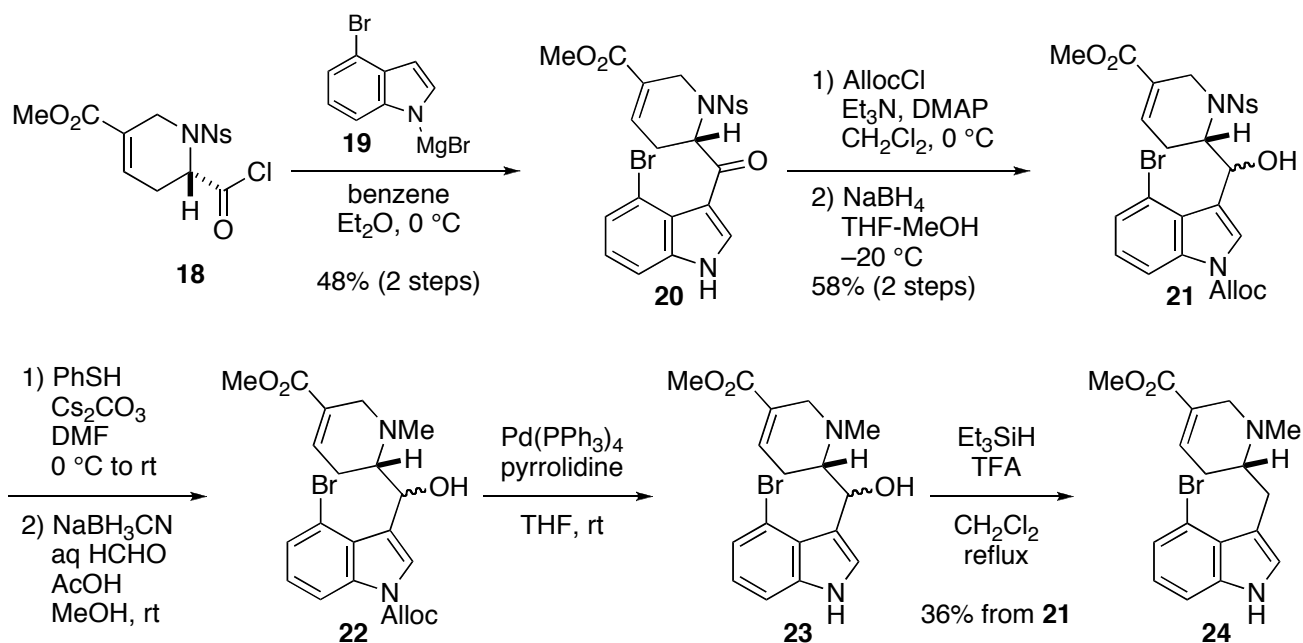


Scheme 3

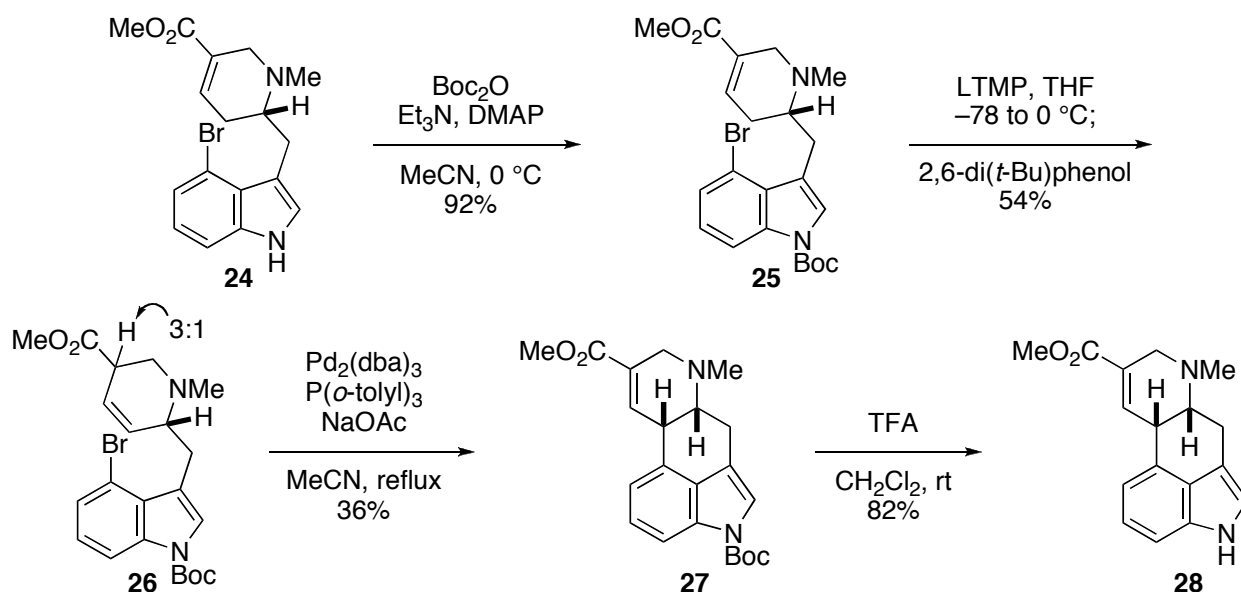
The crucial coupling between the D ring and the indole units was effected by acylation of the magnesium salt of 4-bromoindole (Scheme 4).¹⁰ Thus, deprotonation of 4-bromoindole with ethylmagnesium bromide and subsequent addition of acid chloride **18** provided coupling product **20** in moderate yield. We next focused on reduction of the carbonyl functionality. Since a direct reduction of the ketone in **20** could not be achieved due to the electron-donating nature of the indole nitrogen, an Alloc group was introduced at the indole nitrogen to activate the carbonyl group. As expected, reduction of the *N*-Alloc compound proceeded smoothly to furnish a diastereomeric mixture of secondary alcohol **21**. Removal of the Ns group and subsequent reductive methylation afforded **22**.¹¹ After cleavage of the Alloc group, deoxygenation of the alcohol was achieved with triethylsilane under acidic conditions to give **24**.¹²

After protection of the indole NH with a Boc group, isomerization of the double bond was performed (Scheme 5). Thus, successive treatment of α,β -unsaturated ester **25** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) and quenching with a bulky phenol, 2,6-di(*t*-Bu)phenol, furnished β,γ -unsaturated ester **26** with a 3:1 diastereoselectivity. The diastereomers were separated and each

isomer was subjected to a Heck reaction. While the attempted Heck reaction of the minor isomer resulted in the formation of an intractable mixture, the major isomer gave **27**, suggesting that the isomerization afforded the desired *trans* isomer as the major isomer. Finally, the Boc group was cleaved with trifluoroacetic acid to give **28**,¹³ which, according to the Oppolzer's procedure,^{2c} can be transformed into lysergic acid.



Scheme 4.



Scheme 5

In summary, we have successfully constructed the tetracyclic ergoline skeleton, which features an acylation at the C3 position of the indole as well as an intramolecular Heck reaction. The optically active

D ring unit was synthesized by a disrotatory electrocyclic reaction of a dibromocyclopropane, which, to the best of our knowledge, is the first example of an optically active dihydropyridine prepared from L-pyroglutamic acid.

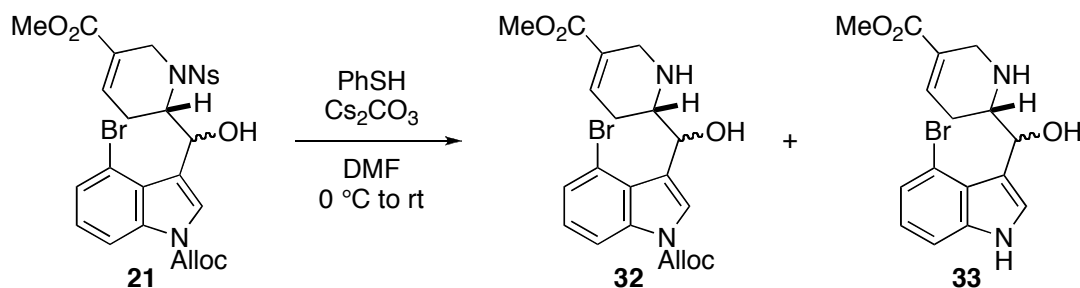
ACKNOWLEDGEMENTS

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8. **17**: $[\alpha]_D^{24} +7.46$ (*c* 0.44, CHCl_3); IR (film) 1718, 1544, 1439, 1370, 1281, 1168, 1120, 1095, 1062, 762 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 8.09-8.12 (m, 1H), 7.58-7.75 (m, 3H), 7.00 (br s, 1H), 4.99 (t, $J = 3.2$ Hz, 1H), 4.31 (d, $J = 15.6$ Hz, 1H), 4.11 (d, $J = 15.6$ Hz, 1H), 3.75 (s, 3H), 2.86 (br s, 2H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 175.6, 164.7, 147.6, 134.6, 133.9, 131.9, 131.8, 131.0, 126.6, 124.6, 52.2, 52.0, 41.5, 27.9; HRMS (FAB) Calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}_8\text{S}$ (M^+): 370.0471, Found: 370.0475.
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11. While removing the Ns group, partial cleavage of the Alloc group concomitantly occurred to afford a mixture of **32** and **33**. **33** could be converted into **23** via a reductive amination (NaBH_3CN , AcOH, aq HCHO, MeOH, rt).



12. **24**: $[\alpha]_D^{24} -15.7$ (*c* 0.38, CHCl_3); IR (film) 2949, 2925, 1700, 1653, 1437, 1397, 1336, 1305, 1267, 1192, 1158, 1141, 1098, 1067, 1042, 1025, 911, 800, 768 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 8.30 (br, 1H), 7.29 (d, $J = 7.8$ Hz, 1H), 7.26 (s, 1H), 7.05 (br, 1H), 7.00 (t, $J = 7.8$ Hz, 1H), 6.98 (br, 1H), 3.75 (s, 3H), 3.56 (dd, $J = 14.1, 4.1$ Hz, 1H), 3.52 (dd, $J = 17.2, 3.4$ Hz, 1H), 3.35 (dd, $J = 17.2, 3.4$ Hz, 1H), 3.16-3.19 (m, 1H), 2.75 (dd, $J = 14.1, 10.3$ Hz, 1H), 2.60 (s, 3H), 2.20 (s, 2H); $^{13}\text{C NMR}$ (CDCl_3 , 100 MHz) δ 166.4, 137.6, 137.6, 128.0, 125.4, 124.6, 124.1, 122.8, 114.2, 113.7, 110.6, 57.6, 51.6, 51.2, 41.0, 28.7, 25.6; HRMS (FAB) Calcd for $\text{C}_{17}\text{H}_{19}\text{BrN}_2\text{O}_2$ (M^+): 362.0630, Found: 362.0632.
13. **28**: $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 7.90 (br, 1H), 7.26 (d, $J = 7.2$ Hz, 1H), 7.21 (d, $J = 7.2$ Hz, 1H), 7.08 (s, 1H), 7.01 (t, $J = 7.2$ Hz, 1H), 6.88 (s, 1H), 4.10 (s, 1H), 3.70 (s, 3H), 3.52 (d, $J = 18.4$ Hz, 1H), 3.49-3.40 (m, 3H), 3.38 (d, $J = 18.4$ Hz, 1H), 3.02 (dd, $J = 14.7, 4.6$ Hz, 1H), 2.77 (dd, $J = 14.7, 11.9$ Hz, 1H), 2.63 (s, 3H); HRMS (FAB) Calcd for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$ (M^+): 281.1290, Found: 281.1284.