ORGANIC LETTERS

XXXX
Vol. XX, No. XX
000–000

Total Synthesis of Lysergic Acid

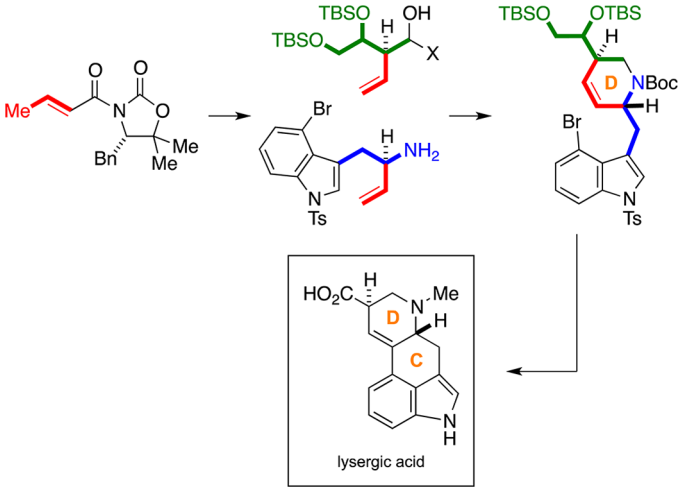
Satoshi Umezaki,[†] Satoshi Yokoshima,[‡] and Tohru Fukuyama*[,‡]

Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan, and Graduate School of Pharmaceutical Sciences, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8601, Japan

fukuyama@ps.nagoya-u.ac.jp

Received July 10, 2013

ABSTRACT



A total synthesis of lysergic acid was accomplished. Key features of our synthesis include stereoselective construction of the stereogenic centers at the allylic positions by using the Evans aldol reaction, and a sequential process with a ring-closing metathesis and an intramolecular Heck reaction to construct the C and D rings.

Lysergic acid (**1**) is a compound obtained by alkaline hydrolysis of ergot alkaloids. Ergot alkaloids are a class of pharmacologically important natural products that exhibit a wide spectrum of biological activities.[1] These molecules have long been the targets of numerous synthetic studies because they have a unique tetracyclic ergoline skeleton containing a tetrahydropyridine and a [*cd*]-fused indole. As a result, a variety of total syntheses and synthetic studies toward lysergic acid and the related ergot alkaloids have been reported to date.[2] Our own synthetic studies toward lysergic acid feature an intramolecular Heck reaction to construct the C ring.[3] In addition, the stereochemistry of the D ring unit must be controlled to carry out the crucial Heck reaction. Herein we disclose an efficient construction of the D-ring unit by means of an Evans aldol reaction and subsequent completion of the total synthesis of lysergic acid.

Our retrosynthesis is shown in Scheme 1. Lysergic acid would be derived from **2** via an intramolecular Heck reaction. The tetrahydropyridine ring in **2** could be formed

[†] University of Tokyo.
[‡] Nagoya University.

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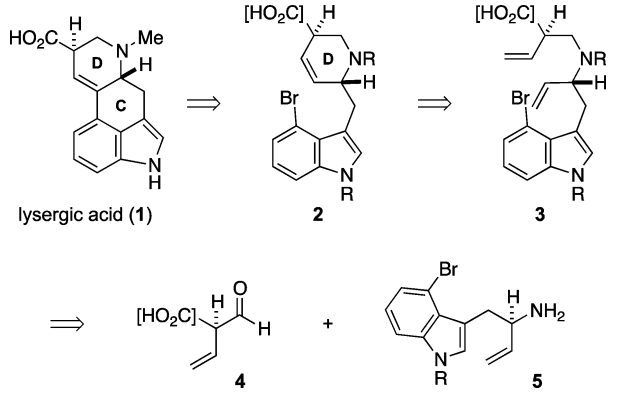
10.1021/ol4019562

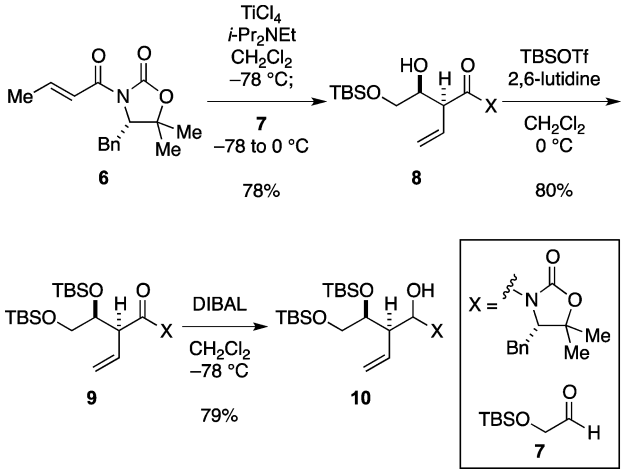
through a ring-closing metathesis of diene **3**,[4] which would be prepared by reductive amination of aldehyde **4** with amine **5**. This retrosynthesis addressed the issue of setting the requisite stereochemistry in intermediate **2** by preparation of the simple units with the proper stereogenic centers at the allylic positions.

Scheme 1. Retrosynthesis



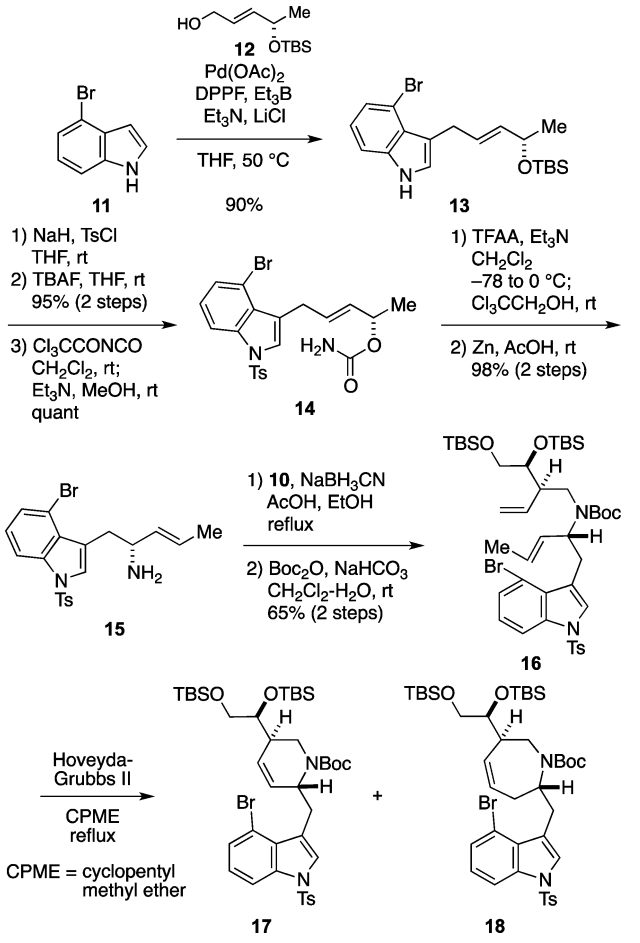
Our synthesis commenced with preparation of the synthetic equivalent of aldehyde **4** by means of the Evans aldol reaction (Scheme 2).[5] Treatment of **6** with titanium tetrachloride and *N*,*N*-diisopropylethylamine generated a titanium enolate,[6] which, upon addition of aldehyde **7**, gave adduct **8** as the sole isomer. After protection of the secondary hydroxy group with a TBS group, the carbonyl group in **9** was partially reduced with DIBAL to afford isolable hemiaminal **10** in 79% yield.

Scheme 2. Synthesis of **10**



We next prepared the requisite amine unit. According to the procedure developed by Tamaru and co-workers,[7] allylation of 4-bromoindole (**11**) with chiral allyl alcohol **12**[8] was carried out (Scheme 3). Protection of the indole NH, followed by cleavage of the TBS ether, afforded an alcohol, which was converted into carbamate **14**. Treatment of **14** with TFAA induced formation of a cyanate,[9] which underwent a [3,3]-sigmatropic rearrangement to afford an isocyanate.[10] The isocyanate was converted into allylamine **15** via the Troc-protected intermediate.

Scheme 3. Attempted Ring-Closing Metathesis



We next focused on the coupling of the amine and aldehyde equivalents in preparation for the subsequent ring-closing metathesis. Reductive alkylation of amine **15** with hemiaminal **10** followed by protection of the resulting

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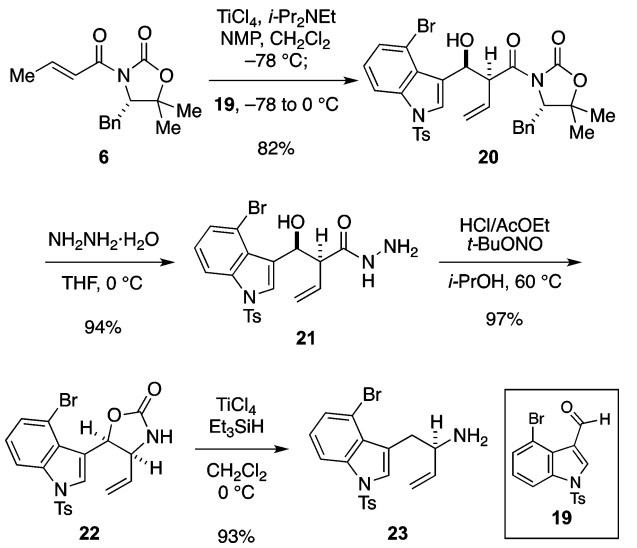
adduct with a Boc group gave **16** in 65% yield over the two steps. Subsequent ring-closing metathesis of **16**, however, proved to be challenging. Treatment of **16** with the second-generation Hoveyda–Grubbs catalyst provided an inseparable mixture of the desired product **17** and byproduct **18** with a seven-membered ring.[11] Completion of the metathesis reaction required prolonged heating because both olefins of **16** are situated in the sterically demanding environment. The harsh reaction conditions resulted in decomposition of the ruthenium catalyst, leading to the formation of **18** via isomerization of the disubstituted double bond. Although the methyl group was important for the asymmetric preparation of the amine unit **15**, it caused an unavoidable problem for the metathesis reaction. We therefore decided to prepare a substrate without the methyl group. During the course of these investigations,[12] we envisioned that the Evans aldol reaction of **6** could effectively control the stereochemistry at the allylic position.

With this idea in mind, we carried out the Evans aldol reaction of **6** with 4-bromo-3-formyl-1-tosylindole

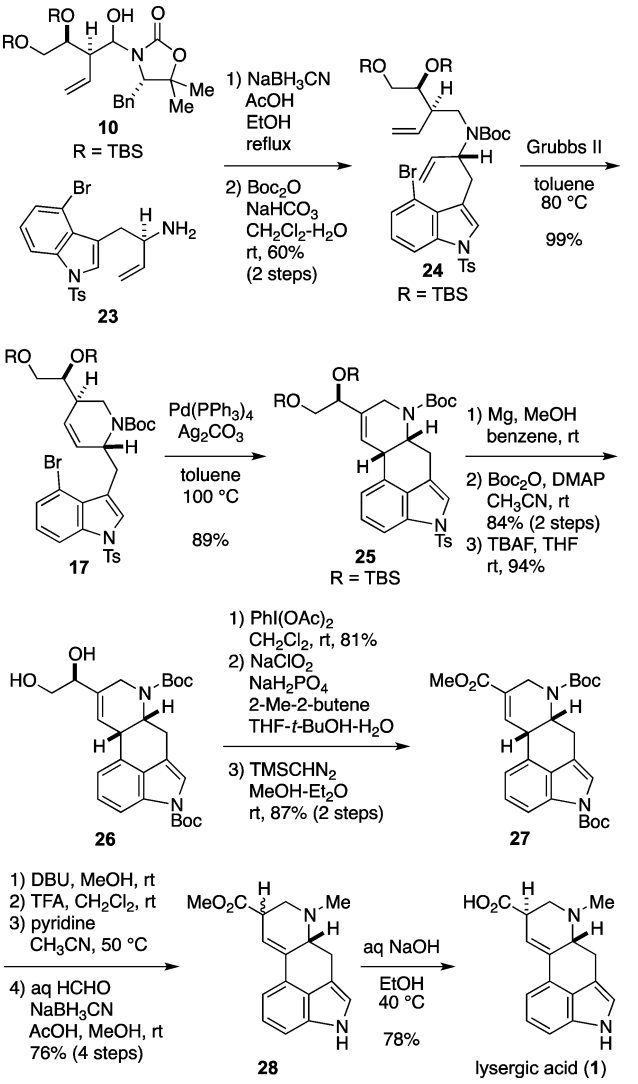
Scheme 4. Synthesis of **23**



(**19**, Scheme 4).[2n,5a,5c,6] The reaction proceeded smoothly to afford adduct **20** as the sole isomer. While attempted ammonolysis of the chiral auxiliary was accompanied by a retro-aldol reaction, treatment of **20** with hydrazine cleanly afforded the corresponding hydrazide **21** in 94% yield. Upon heating with *tert*-butyl nitrite under acidic conditions, **21** was converted into an acyl azide,[13] which underwent a Curtius rearrangement under the same conditions to give oxazolidinone **22** in 97% yield. Deoxygenation was effected by treatment of **22** with triethylsilane and titanium tetrachloride to give allylamine **23**.

Reductive alkylation of amine **23** with hemiaminal **10**, followed by protection of the resulting amine with a Boc group, gave **24** in 60% yield (Scheme 5). As expected, the crucial ring-closing metathesis with the second-generation Grubbs catalyst[14] proceeded smoothly to afford **17** in a nearly quantitative yield. The stereoselective construction of the D ring was effectively accomplished, and the subsequent intramolecular Heck reaction proceeded uneventfully to give **25** in good yield.

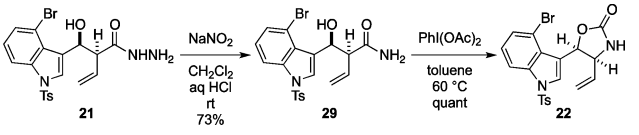
Scheme 5. Synthesis of Lysergic Acid



(11) The presence of **18** was detected by mass spectrum analysis of the inseparable mixture of the products. In addition, two pairs of peaks which could be assigned as the olefin were obsereved in the ^{1}H NMR spectrum.

(12) In our case, the asymmetric Overman rearrangement using (*R*)-COP-Cl did not yield reproducible results. Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412.

(13) Treatment of **21** with sodium nitrite in a mixture of CH_2Cl_2 and aq HCl furnished carboxamide **29**, which could also be converted into **22** via Hofmann rearrangement. Cf. Honzl, J.; Rudinger, J. *Collect. Czech. Chem. Commun.* **1961**, *26*, 2333.



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Further functional group manipulations led to the completion of the total synthesis of lysergic acid (**1**). Thus, after switching from the Ts group to a Boc group, the TBS protecting groups were removed by treatment with TBAF. The resulting 1,2-diol **26** was oxidatively cleaved with (diacetoxyiodo)benzene to afford an aldehyde, which was converted in two steps into methyl ester **27**.[15] Ester **27** was converted into lysergic acid according to the literature procedure.[2k,3a] The double bond underwent isomerization under the basic conditions to furnish a β,γ-unsaturated ester. After cleavage of the Boc groups with TFA, the resulting secondary amine was subjected to reductive methylation with formalin to give **28**. Finally, hydrolysis of the methyl ester furnished lysergic acid (**1**).

In summary, we have achieved the total synthesis of lysergic acid in 19 steps and 12% overall yield from the known substrate **6**. Key features of our synthesis include stereoselective construction of the stereogenic centers at the allylic positions by using the Evans aldol reaction, and a sequential process with a ring-closing metathesis and an intramolecular Heck reaction to construct the C and D rings.

Acknowledgment. This work was financially supported by JSPS KAKENHI Grant Numbers 20002004, 25221301, the Research Foundation for Pharmaceutical Sciences, the Mochida Memorial Foundation for Medical and Pharmaceutical Research, and the Uehara Memorial Foundation. S.U. was a Research Fellow of JSPS.

Supporting Information Available. Experimental details and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charges via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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