ORGANIC LETTERS

2008
Vol. 10, No. 22
5239−5242

Total Synthesis of (±)-Lysergic Acid, Lysergol, and Isolysergol by Palladium-Catalyzed Domino Cyclization of Amino Allenes Bearing a Bromoindolyl Group

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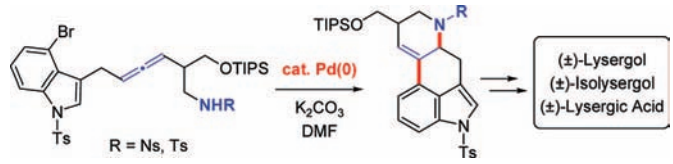
Received September 29, 2008

ABSTRACT



Ergot alkaloids and their synthetic analogs have been reported to exhibit broad biological activity. We investigated direct construction of the C/D ring system of ergot alkaloids based on palladium-catalyzed domino cyclization of amino allenes. With this biscyclization as the key step, total synthesis of (±)-lysergic acid, (±)-lysergol, and (±)-isolysergol was achieved.

Ergot alkaloids are pharmacologically important indole alkaloids produced by the fungus *Claviceps purpurea*, which grows parasitically on rye and other grains (Figure 1).[1] These alkaloids have been reported to exhibit broad biological activity, and several synthetic derivatives such as pergolide or bromocriptine are also used as antiprolactin and anti-Parkinson's disease drugs.[2] Owing to their biological importance, ergot alkaloids, particularly lysergic acid (**1**), have been the target of many synthetic studies, but most of the previous syntheses relied on a stepwise linear approach for construction of the C/D ring system.[3]

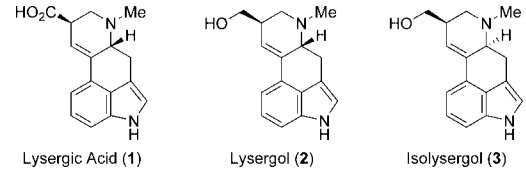


Figure 1. Indole alkaloids of the ergot family.

One exception is Oppolzer's strategy, which is based on simultaneous construction of C/D rings by an intramolecular imino-Diels−Alder reaction.[3d]

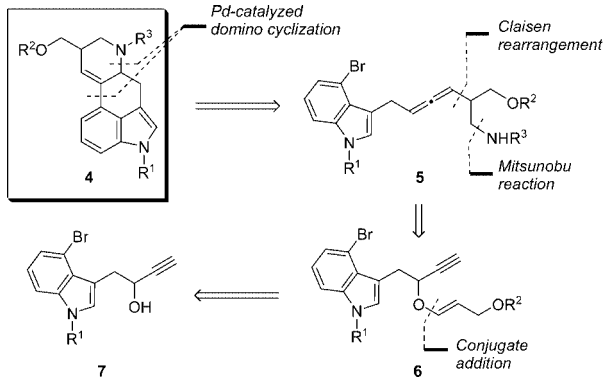
We expected domino cyclization of allenes of the type **5** (Scheme 1) to provide direct access to the core structure of ergot alkaloids **4**, including lysergic acid (**1**), lysergol (**2**), and isolysergol (**3**). In recent years, transition-metal-catalyzed cyclization of allenes bearing a nucleophilic functionality has been widely used for construction of various types of heterocycles, and several efficient domino cyclizations of

(1) For isolation of lysergic acid, see: (a) Jacobs, W.; Craig, L. *J. Biol. Chem.* **1934**, *104*, 547–551. (b) Stoll, A.; Hofmann, A.; Troxler, F. *Helv. Chim. Acta* **1949**, *32*, 506–521. For isolation of lysergol, see: (c) Agurell, S. *Acta Pharm. Suec.* **1965**, *2*, 357–374. For isolation of isolysergol, see. (d) Agurell, S. *Acta Pharm. Suec.* **1966**, *3*, 7–10.

(2) (a) Ninomiya, I.; Kiguchi, T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, CA, 1990; Vol. 38, pp 1−156. (b) *The Merck Index*, 12th ed.; Merck and Co., Inc.: Whitehouse Station, NY, 1996; pp 231. (c) Somei, M.; Yokoyama, Y.; Murakami, Y.; Ninomiya, I.; Kiguchi, T.; Naito, T. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: San Diego, CA, 2000; Vol. 54, pp 191−257.

10.1021/ol8022648 CCC: $40.75 © 2008 American Chemical Society
Published on Web 10/29/2008

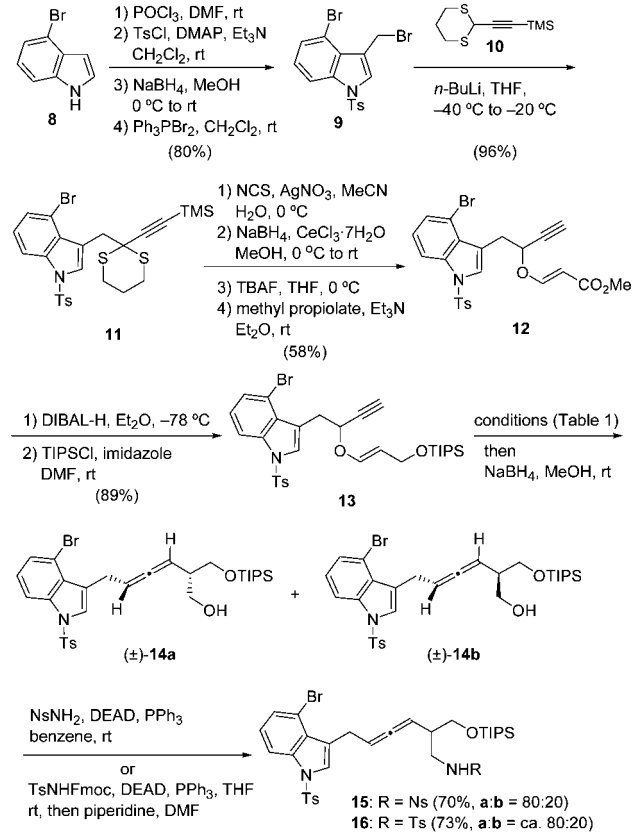
Scheme 1. Retrosynthetic Analysis of **4**



amino allene derivatives have also been reported.[4,5] However, the reaction of allenes having an aryl halide and amino group at both ends of internal allenes is unprecedented. We describe herein a new entry to the ergot alkaloids skeleton using a palladium-catalyzed domino cyclization of amino allenes **5** bearing a protected 4-bromoindol-3-yl group. Total synthesis of lysergic acid, lysergol, and isolysergol using this strategy is also presented.

Retrosynthetic analysis of the amino allenes **5** is shown in Scheme 1. We envisioned that the allene unit of **5** can be constructed by Claisen rearrangement of enol ether **6**, which could be readily obtained by conjugate addition of propargyl alcohol **7** to methyl propiolate followed by reduction/protection.

Scheme 2. Synthesis of Allenic Amides **15** and **16**



Preparation of the requisite allenic amides of the type **5** for the palladium-catalyzed domino cyclization is outlined in Scheme 2. 3-(Bromomethyl)indole **9** is easily accessible from commercially available 4-bromoindole **8**.[6] Lithiation and addition of 1,3-dithiane **10**[7] to the bromide **9** gave thioacetal **11** in 96% yield. Subsequent functional-group modifications, including hydrolysis of the thioacetal,[8] reduction, desilylation, and conjugate addition to methyl propiolate, provided the enoate **12**.[9] The propargyl vinyl ether **13** was obtained by DIBAL reduction and silylation of **12**. Claisen rearrangement under thermal conditions (*m*-xylene, 170 °C) gave the desired allenic alcohol **14** (**a**:**b** = ca. 33:67) in only 38% yield (Table 1, entry 1). Microwave irradiation[10] in $CHCl_3$ dramatically improved the yield to 82% (entry 2).[11] Furthermore, use of 5 mol % of gold-oxo complex $[(Ph_3PAu)_3O]BF_4$ resulted in 78% yield of **14**, in favor of the opposite diastereomer (**a**:**b** = ca. 80:20, entry 3).[12] Mitsunobu reaction of **14** with $NsNH_2$ or TsNHFmoc[13] (followed by piperidine treatment) gave *N*-nosyl and *N*-tosylamide derivatives **15** and **16** (**a**:**b** = 80:20), respectively.

We next investigated construction of the ergot alkaloid skeleton via the palladium-catalyzed domino cyclization

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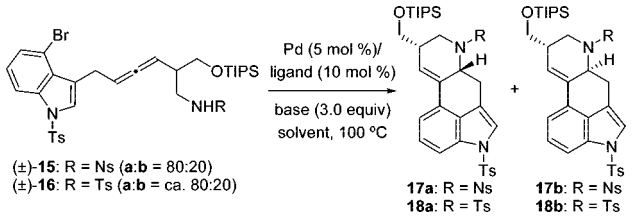
Table 1. Claisen Rearrangement of Propargyl Ether **13**

entry	conditions[a]	yield (%)[b]	dr (**a**:**b**)[c]
1	*m*-xylene, 170 °C, 50 min	38	ca. 33:67
2	$CHCl_3$, MW, 120 °C, 12 min then 150 °C, 12 min	82	ca. 33:67
3	$[(Ph_3PAu)_3O]BF_4$ (5 mol %) CH_2Cl_2, 40 °C, 10 h	78	ca. 80:20

[a] MW = microwave irradiation. [b] Isolated yields after reduction with $NaBH_4$. [c] Determined by HPLC and ^1H NMR analysis.

Table 2. Palladium-Catalyzed Domino Cyclization[a]



(±)-**15**: R = Ns (**a**:**b** = 80:20)
(±)-**16**: R = Ts (**a**:**b** = ca. 80:20)

17a: R = Ns
18a: R = Ts

17b: R = Ns
18b: R = Ts

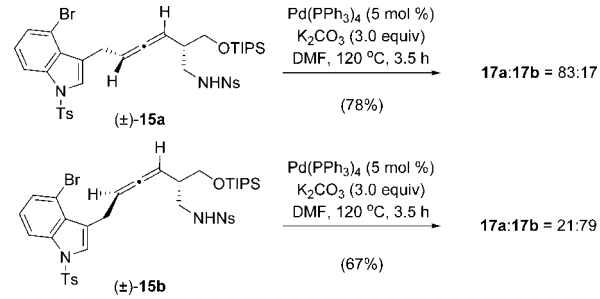
entry	Pd/ligand	solvent	base	yield (%)[b]	dr (**a**:**b**)[c]
1	$Pd(PPh_3)_4$	DMF	Na_2CO_3	31	84:16
2	$Pd(PPh_3)_4$	DMF	Cs_2CO_3	41	75:25
3	$Pd(PPh_3)_4$	DMF	K_2CO_3	83	73:27
4[d]	$Pd(PPh_3)_4$	DMF	K_2CO_3	78	74:26
5	$Pd(PPh_3)_4$	toluene	K_2CO_3	trace	ND[f]
6	$Pd(PPh_3)_4$	dioxane	K_2CO_3	68	80:20
7[d]	$Pd(PPh_3)_4$	DMSO	K_2CO_3	68	74:26
8	$Pd(OAc)_2/PPh_3$	DMF	K_2CO_3	61	88:12
9	$PdCl_2$(dppf)	DMF	K_2CO_3	41	92:8
10	$Pd(OAc)_2/P(o\text{-tol})_3$	DMF	K_2CO_3	20	>95:5
11[e]	$Pd(OAc)_2$/*rac*-BINAP	DMF	K_2CO_3	31	72:28
12[g]	$Pd(PPh_3)_4$	DMF	K_2CO_3	65	87:13

[a] Reactions were carried out using a diastereomixture of **15** or **16** (**a**:**b** = 80:20) at 0.06 M for 2.5−5 h. [b] Isolated yields. [c] Determined by ^1H NMR analysis. [d] Reaction was performed at 120 °C. [e] Reactions were carried out using Pd (5 mol %) and ligand (5 mol %) [f] Not determined. [g] Reaction was carried out using a substrate **16** at 120 °C.

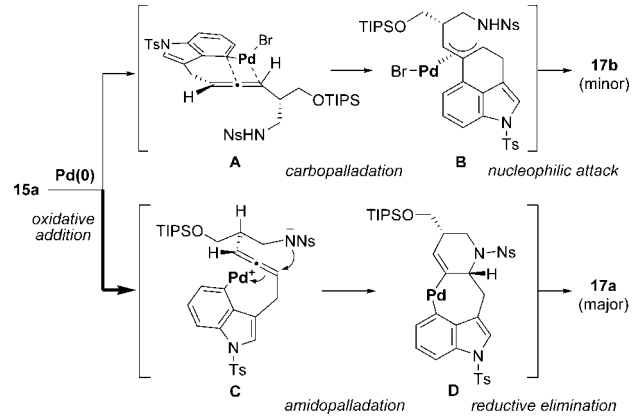
(Table 2). The reaction was conducted using a 80:20 diastereomixture of **15** and **16** because separating the diastereomeric mixtures resulting from Claisen rearrangement was difficult. Reaction of **15** with 5 mol % of $Pd(PPh_3)_4$ and Na_2CO_3 in DMF at 100 °C afforded desired product **17** in 31% yield (**a**:**b** = 84:16, entry 1). Among the several bases investigated, K_2CO_3 has proven to be the most effective to give 83% of **17** as a 73:27 diastereomixture (entry 3).[14] Although the reaction at 120 °C slightly decreased the yield of the desired product, unidentified side products were easily removed from the desired product **17** (entry 4). Changing the solvent from DMF to toluene, dioxane or DMSO did not enhance the yield of desired product (entries 5−7). Further screening using $Pd(OAc)_2/PPh_3$ (entry 8), $PdCl_2$(dppf) (entry 9), $Pd(OAc)_2/P(o\text{-tol})_3$ (entry 10) and $Pd(OAc)_2$/*rac*-BINAP (entry 11) was done. As diastereoselectivity improved, yield of desired product decreased (entries 3, 8−10), except for using $Pd(OAc)_2$/*rac*-BINAP (entry 11). When the *N*-tosyl derivative **16** was employed, desired product **18** was isolated in 65% yield with good diastereoselectivity (87:13, entry 12).[15]

To obtain some mechanistic insight of the domino cyclization, diastereomerically pure **15a** and **15b**(obtained by careful HPLC separation of **14** followed by Mitsunobu reaction) were subjected to the reaction conditions shown in entry 4 (Table 2). Domino cyclization of the major isomer **15a** gave an 83:17 diastereomixture, in 78% yield, in which the major cyclized product **17a** predominated (Scheme 3). In contrast, reaction of the minor isomer **15b** favored the diastereomer **17b** (**a**:**b** = 21:79) in 67% yield.

Scheme 3. Palladium-Catalyzed Domino Cyclization of Diastereomerically Pure Substrates

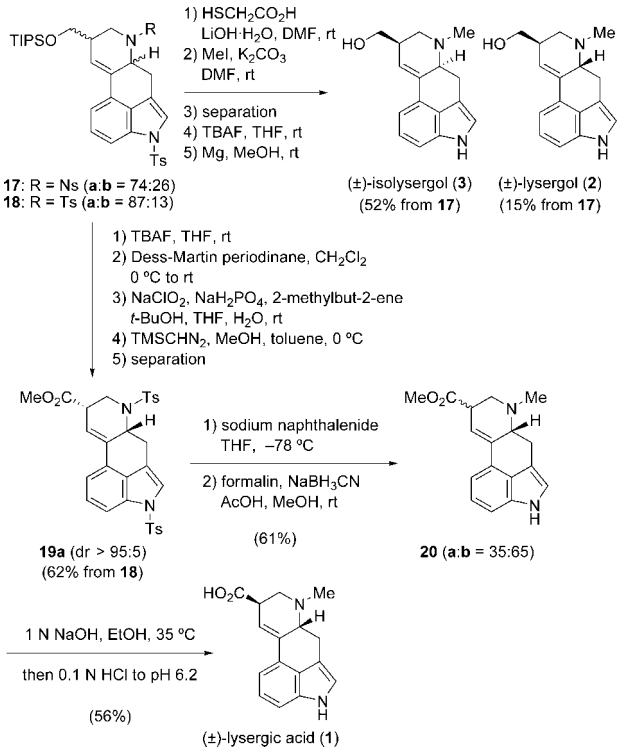


Scheme 4. Proposed Mechanism for Domino Cyclization



A rationale for stereoselectivities of the domino cyclization of internal amino allenes is depicted in Scheme 4. This domino cyclization could proceed through two pathways: (1) carbopalladation[4,5] and (2) amidopalladation.[5b,k] Because of a steric reason, carbopalladation of indolylpalladium(II) bromide, formed in situ by oxidative addition of the bromoindole moiety to Pd(0), would proceed through 6-*exo* type cyclization as depicted in **A** to generate η^3-allylpalladium complex **B**. The second cyclization by the nosylamide group in an *anti* manner then gives the minor isomer **17b**. On the other hand, coordination of the indolylpalladium(II) to the allenic moiety would promote *anti* attack of the nosylamide group as shown in **C** (amidopalladation pathway) to give a palladacycle **D**, which gives the isomer **17a** by reductive elimination. Predominant formation of **17a** can be rationalized by considering the strained bicyclic structure **A** in the carbopalladation step.

Scheme 5. Total Synthesis of Isolysergol (**3**), Lysergol (**2**), and Lysergic Acid (**1**)



With the ergot alkaloid derivatives **17** and **18** bearing the requisite functionalities in hand, the final stage was set for the completion of the total synthesis of lysergic acid, lysergol, and isolysergol (Scheme 5). Deprotection of the Ns group of **17** and *N*-methylation gave a separable mixture of diastereomers, each of which was readily converted into isolysergol (**3**) and lysergol (**2**) by removal of TIPS and Ts groups. We chose tosylamide **18** as the precursor of lysergic acid.[16] Cleavage of the TIPS group of **18**, oxidation of the resulting primary alcohol by standard protocol, and esterification with $TMSCHN_2$ gave the corresponding methyl ester **19a** (62%, 4 steps).[17] Removal of tosyl group with sodium naphthalenide and subsequent *N*-methylation led to a diastereomixture of methyl isolysergate **20a** and lysergate **20b** (35:65). Total synthesis of lysergic acid was completed by hydrolysis of **20** with NaOH, accompanying isomerization to the favorable isomer.[3i] Physical data were in agreement with those of natural and synthetic lysergic acid, lysergol and isolysergol reported in the literature.[3i,j,l]

In conclusion, we developed a novel entry to direct construction of an ergot alkaloid skeleton based on palladium-catalyzed domino cyclization of amino allenes. With this biscyclization as the key step, total synthesis of lysergic acid, lysergol and isolysergol was achieved.

Acknowledgment. This work was supported by a Grant-in-Aid for Encouragement of Young Scientists (A) (H.O.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and Targeted Proteins Research Program. S.I. is grateful to Research Fellowships of the Japan Society for the Promotion of Science (JSPS) for Young Scientists. Appreciation is expressed to Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation (NIBIO).

Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL8022648

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(14) The relative configurations of **17a** and **17b** were confirmed by their conversion to isolysergol and lysergol, respectively.
(15) The relative configurations of **18a** and **18b** were confirmed by derivatization of **17a** and **17b** to the same compounds, respectively (see Supporting Information).
(16) Cleavage of nosyl group in the ester derived from **17** was less effective (20−30% yield) under standard conditions.
(17) The relative configuration of **19a** was confirmed by conversion to **18a** (see Supporting Information).
(18) Gockel, B.; Krause, N. *Org. Lett.* **2006**, *8*, 4485–4488.