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Synthetic Methods

Total Syntheses of Pyroclavine, Festuclavine, Lysergol, and Isolysergol via a Catalytic Asymmetric Nitro-Michael Reaction

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Dedicated to Professor Vinod K. Singh

Abstract: A catalytic enantioselective construction of vicinal stereocenters is reported. The reaction takes advantage of thiourea-catalyzed intramolecular nitronate addition onto α,β-unsaturated ester to afford exceptional levels of enantioselectivity (up to 97% *ee*) with moderate diastereoselectivity (up to 4:1). Using this method, a cross-conjugated ester was synthesized in few steps, from which a 6-*endo-trig* cyclisation led to the formation of all required functionalities for total syntheses of ergot alkaloids. The strategy not only offers first total syntheses of ergot alkaloids, festuclavine (**1c**), and pyroclavine (**1e**), and but also an efficient and general approach to other congeners such as, lysergol (**1b**), and isolysergol (**1d**).

The indole alkaloids of the ergot family (**1a--f**, Figure 1) have been the subject of longstanding interest,[1] because of their striking physiological properties. These are one of the most prolific groups of alkaloids derived from the fungus *Claviceps purpurea* on rye grain. The potential of this group of alkaloids as medicinal agents is very high based on their broad pharmacological activity, responding like physiologically important biosubstances as noradrenaline, serotonin and/or dopamine to their receptors.

Their structures are typically designated as an ergoline alkaloid having the characteristic structure of a tetracyclic indole ring system. Biosynthetically derived from tryptophan through intriguing enzymatic pathways,[2] total synthesis of several members of this class of natural compounds have been reported.[3] These molecules have long been the targets of numerous synthetic studies because they have a unique tetracyclic ergoline skeleton containing a tetrahydropyridine and a fused indole. Consequently, the construction of the synthetically challenging tetrahydrobenzo[c,d]indole scaffold has recently received considerable attention, even in its racemic forms.[4]

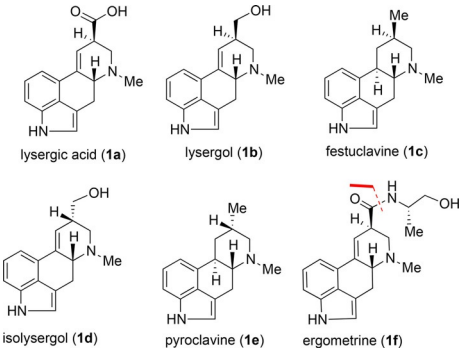
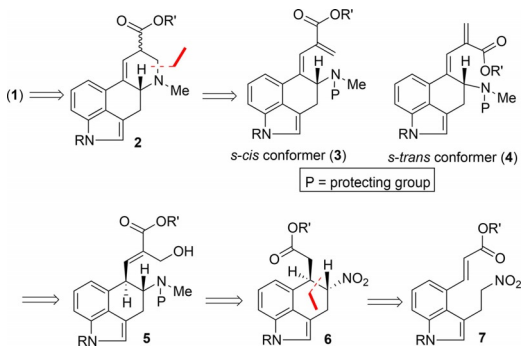


Figure 1. Selected ergot alkaloids **1a--f**.

Retrosynthetically, we envisioned that a unified approach to the ergot alkaloids can be established by a key unprecedented 6-*endo-trig* cyclisation of cross-conjugated α,β-unsaturated ester (Scheme 1). We argue that a cross-conjugated α,β-unsaturated ester can exist as two different conformations such as *s-cis* and *s-trans* (see **3**–**4**, Scheme 2). These conformers have potential to afford two different tetracyclic intermediates such as **2** and **9**. A 6-*endo-trig* cyclisation of *s-cis* conformer **3** via *aza*-Michael reaction can provide tetracycle **2**, on the other hand *s-trans* conformer **4** can afford cross-conjugated lactam **9** essentially following a 6-*exo-trig* cyclisation (Scheme 2). Therefore, a selective cyclisation under an optimized condition would be interesting and worth testing.



Scheme 1. Retrosynthetic analysis of ergot alkaloids **1**–**2**.

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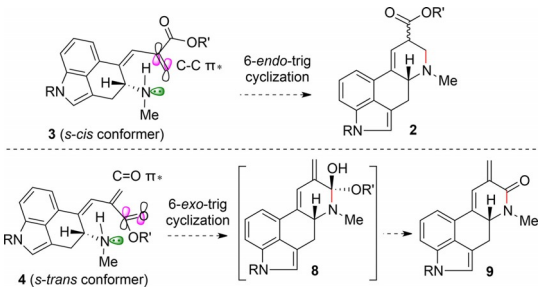


Scheme 2. Working hypothesis.

We imagined that compound **3** can be accessed from tricyclic γ-nitroester derivative **6** via ester **5** following synthetic manipulation, which in turn can be synthesized from another key Michael addition of nitronate[5] onto conjugated esters (see **7**) in an intramolecular fashion.[6]

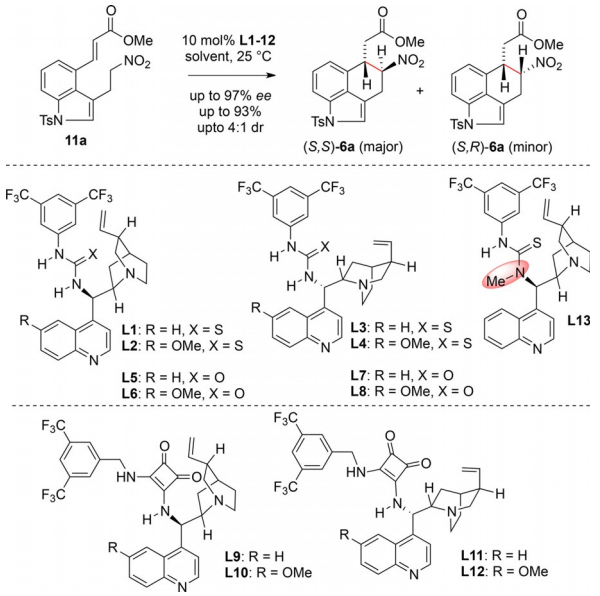
The asymmetric Michael reaction is one of the most powerful carbon–carbon bond-forming reactions available to the organic chemist and remains an important challenge within organic synthesis.[7] Since the start of the new millennium, much work has focused on asymmetric organocatalytic processes.[8] In most cases, the Michael acceptor is almost always a conjugated enone, enal, or nitroalkene variant.[9,10] In the context of total synthesis of ergot alkaloids, we were particularly drawn to the use of nitronates in the intramolecular Michael addition to conjugated esters as an entry to cyclic constrained γ-amino acids (Scheme 1).

On the basis of previous studies using nitronates as nucleophiles by Cobb,[6a,11] we decided to investigate the potential of chiral bifunctional organocatalysts in this process and thus screened a range of thiourea[12] and squaramide catalysts[13] (Table 1). We anticipated that the thiourea needs to coordinate to both the nitro group (essentially a nitronate generated in situ by abstraction of α-proton by quinuclidine base) and the ester to activate the system and allow the reaction to proceed.[14] This can only occur effectively with the '*E* ester" and stabilizes **TS (10)** as favored transition state (Figure 2) through the H-bonding via three acidic N–H groups of the protonated catalyst.[14,15]

However, to have optimum results, a balance between steric and electronic effects has to be maintained. In fact, a bulky ester might disturb the H-bonding [see, **TS** (**10**)], whereas an electron-releasing group at indole nitrogen might reduce the reactivity of α,β-unsaturated ester. We imagined that a suitable electron-withdrawing group at indole nitrogen such as sulfonyl or Boc group would ease the reaction by pulling electrons towards it and create the proper electronic environment (Figure 2).

At the outset, we carried out optimization reaction of **11a** in the presence of 10 mol% catalyst **L1** (synthesized from cinchonine) in different solvents at room temperature. We were delighted to obtain cyclized product **6a** in dichloromethane in 82% yields with 2.7:1 d.r. and 97% *ee* in favor of (*S*,*S*)-**6a** (entry 1).[16,17] Under similar condition, chloroform also afforded **6a** in similar efficiency (entry 2). The yield and diastereoselectivity can be improved to 93% and 3:1, respectively, by running reaction in dichloroethane (entry 3). Using other solvents, such as tetrahydrofuran and EtOAc, makes the reactions sluggish, although high enantioselectivity (96% *ee*) and d.r. (up to 3.7:1) were obtained (entries 4–5). The reaction in acetonitrile was shown to give the best balance among yield, diastereoselectivity, and enantioselectivity (entry 6). By lowering the temperature to 0 °C, product **6a** was obtained in 71% yields with 3.7: 1 d.r. and 97% enantioselectivity (entry 7). Increasing the temperature to 40 °C resulted in deterioration of enantioselectivity to 86% *ee* (entry 8). By lowering catalyst loading to 5 mol%, we isolated **6a** in only 69% yields with 2.8: 1 d.r. and 91% *ee* (entry 9). Therefore, further optimizations were carried out using 10 mol% catalysts **L2**–**L8** in dichloroethane at room

Table 1. Optimization of TU-catalyzed Michael reaction of nitronate.



S. No	Catalyst [mol%][a]	Solvent	*t* [d]	Yield (**6**) [%][b]	*ee* [%]	d.r. (a:b)
1	10 **L1**	CH_2Cl_2	5	82	97	2.7:1
2	10 **L1**	$CHCl_3$	5	76	97	2.8:1
3	10 **L1**	$(CH_2Cl)_2$	5	93	95	3:1
4	10 **L1**	THF	10	50	96	3.6:1
5	10 **L1**	EtOAc	7	72	96	3.7:1
6	10 **L1**	CH_3CN	10	60	93	4:1
7[c]	10 **L1**	$(CH_2Cl)_2$	7	71	97	3.7:1
8[d]	10 **L1**	$(CH_2Cl)_2$	2	90	86	2.4:1
9	5 **L1**	$(CH_2Cl)_2$	7	69	91	2.8:1
10	10 **L2**	$(CH_2Cl)_2$	5	87	86	2.5:1
11	10 **L3**	$(CH_2Cl)_2$	5	90	−93	2.8:1
12	10 **L4**	$(CH_2Cl)_2$	5	85	−88	2.7:1
13	10 **L5**	$(CH_2Cl)_2$	5	87	88	2.4:1
14	10 **L6**	$(CH_2Cl)_2$	5	89	87	2.6:1
15	10 **L7**	$(CH_2Cl)_2$	5	87	−86	2.7:1
16	10 **L8**	$(CH_2Cl)_2$	5	85	−84	2.4:1
17	10 **L9**	$(CH_2Cl)_2$	5	89	81	3.1:1
18	10 **L10**	$(CH_2Cl)_2$	5	85	−84	3.4:1
19	10 **L11**	$(CH_2Cl)_2$	5	93	−85	3.2:1
20	10 **L12**	$(CH_2Cl)_2$	5	91	79	3.1:1

[a] Reactions were carried out on a 0.047 mmol of **11a** with 0.0047 mmol (10 mol%) of catalyst **L** in 2 mL of solvent at specified temperature and specified time. [b] Isolated yields of **6a** after column chromatography. [c] Reaction was carried out at 0 °C. [d] Reaction was carried out at 40 °C.

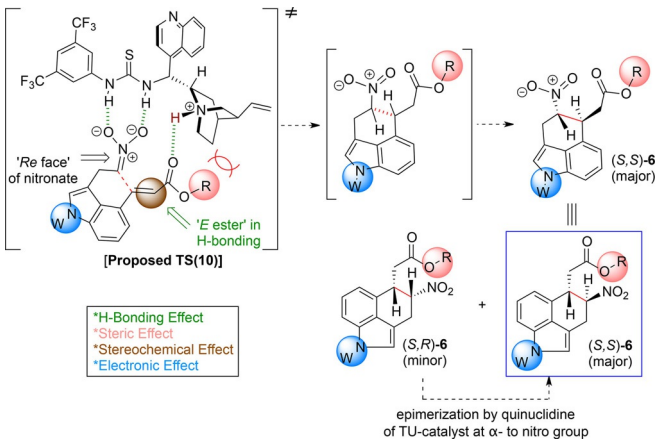


Figure 2. Stereochemical rational using thiourea **L1**.[14].

temperature (entries 10–16). Interestingly, the use of cinchonidine-derived catalyst **L3** gave the oppositely configured product, as compared to cinchonine-derived catalyst **L1**, in almost identical yield, diastereoselectivity, and enantioselectivity (entry 11). This ensures the synthetic approaches to either antipodes of ergot alkaloids. Encouraged by Rawal's[13] elegant work on squaramide-catalyzed Michael addition of 1,3-dicarbonyls onto β-nitrostyrene, further studies were conducted using 10 mol% of bifunctional squaramide catalysts[13] **L9**–**L12** in dichloroethane at room temperature (entries 17–20). However, these catalysts afforded product **6a** in up to 85% *ee* with 3.4: 1 d.r. with good yields (entries 18–19). Gratifyingly, our intramolecular Michael reaction can be performed on 1 g scale of compound **11a** using 5 mol% **L1** catalyst at 25 °C (20 mL dichloroethane), which afforded product (*S*,*S*)-**6a** (≈7 d) in 86% yield with 93% *ee* (d.r. = 3:1).[18]

With the standard condition (Figure 3), we then probed the catalytic enantioselective intramolecular Michael reaction in

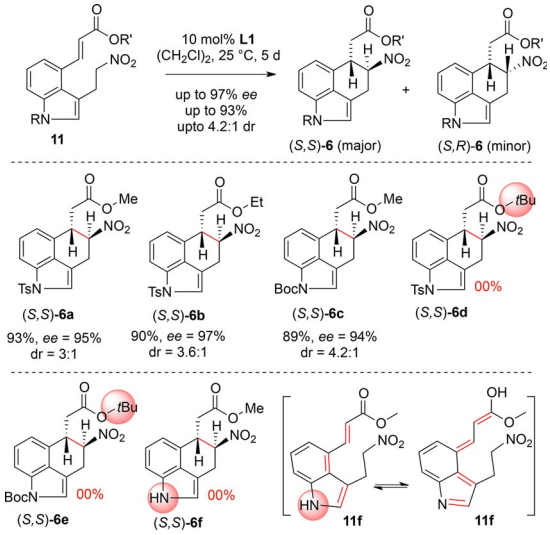
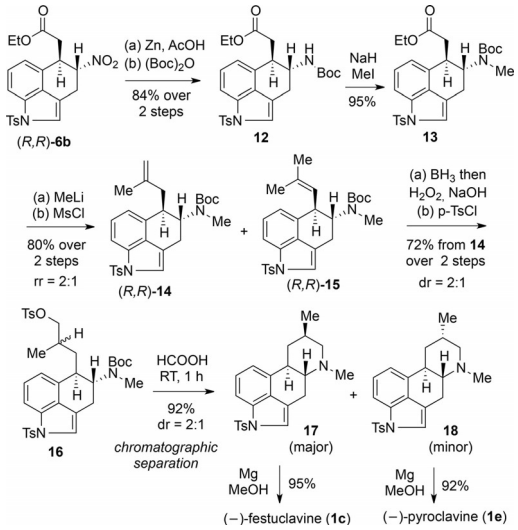


Figure 3. Substrates scope of Michael reactions. [a] Reactions were carried out on a 0.5 mmol of **11a**--**f** with 0.05 mmol (10 mol%) of catalyst **L1** in 5 mL of dicholoroethane at 25 °C for 5 days. [b] Isolated yields of **6** after column chromatography.

few substrates and the results are shown in Figure 3. It was observed that methyl and ethyl esters with *N*-protected indoles such as **11a**,**b** and **11c** are excellent substrates and afforded products **6a**--**c** in high yields with excellent enantioselectivities and moderate diastereoselectivities. However, substrates having a bulky *tert*-butyl group such as **11d** and **11e** didn't afford any products. These clearly suggest that bulky ester functionality hampers **TS-10** by disturbing H-bonding. It was also observed that *N*-unprotected indole substrate **11f** failed to afford product under standard condition. This also suggest that *N*-unprotected indole pushed electron density towards the electron-withdrawing α,β-unsaturated ester and get stabilized as shown in Figure 3. Thus, an electron-withdrawing group at the *N* of indole is very much essential for efficient reaction. Further, the effect of H-bonding was checked by utilizing a **L13**, where it is *N*-methylated. It was observed that *N*-free thiourea catalyst is most important factor, thus catalyst **L13** having *N*-methyl group didn't afford any product. This clearly suggests that H-bonding is very much essential for efficient Michael reaction to afford products with best selectivities.

Next, we turned our attention for utilization of major diastereomer (*S*,*S*)-**6b** for total syntheses of ergot alkaloids as per Scheme 3.[17] This efforts resulted in total syntheses of unnatu-



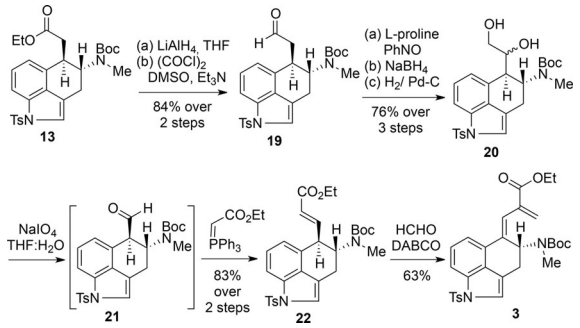
Scheme 3. Total syntheses of festuclavine (**1c**) and pyroclavine (**1e**).

ral (+)-festuclavine (*ent*-**1c**) and (+)-pyroclavine (*ent*-**1e**; see the Supporting Information for details).[17] Therefore, we synthesized (*R*,*R*)-**6b** from **11b** in the presence of 10 mol% of **L3** catalyst (synthesized from cinchonidine) for synthesis of naturally occurring ergot alkaloids. Delightfully, our established condition furnished (*R*,*R*)-**6b** in 91% yield (d.r. = 3.6:1) with 97% *ee*.[18]

Having Michael product (*R*,*R*)-**6b** in hand, we then turned our attention for its utilization for unified approach to the ergot alkaloids (Figure 1). Towards this, we reduced the nitro functionality in presence of Zn, AcOH to give primary amine, which was further reacted with $(Boc)_2O$ to give γ-aminoester

12 in 84% over two steps (Scheme 3). Compound **12** was then *N*-methylated to give **13**, which was then reacted with MeLi followed by treatment with methanesulfonyl chloride to furnish inseparable mixture of olefins **14** and **15** in 2:1 regio isomeric ratio in good yields.[19] Without separation, this mixture was reacted under hydroboration-oxidation followed by tosylation to afford primary tosylate **16** in 72% yield (calculated from **14**) 2:1 d.r. (Scheme 3). It is important to note that the trisubstituted olefin didn't afford any product and which was isolated from the reaction mixture. Compound **16** was further treated with formic acid to affect cyclization to form diastereomers having tetracyclic ring **17** and **18**. Interestingly, these diastereomers are separable in column chromatography and, from which, deprotection of *N*-tosyl (Ts) functionality simply completed first total syntheses of festuclavine (**1 c**) and pyroclavine (**1 e**) in excellent yields (Scheme 3).

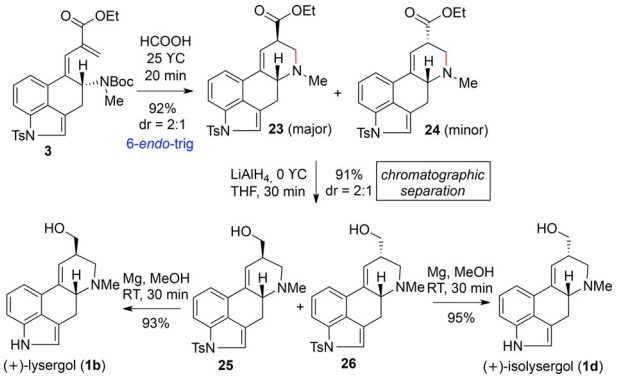
In search for a flexible route to ergot alkaloids, γ-aminoester **13** was converted to aldehyde **19** by $LiAlH_4$ reduction at −10 °C followed by Swern oxidation in 84% over 2 steps (Scheme 4). Aldehyde **19** was subjected further to α-oxygenation using catalytic L-proline and nitrosobenzene, $NaBH_4$ reduction, and hydrogenation, which afforded diol **20** in 76% over 3 steps. Next, diol **20** was oxidatively cleaved using $NaIO_4$ followed by reaction with a stabilized Wittig to afford α,β-unsaturated ester **22**. Gratifyingly, an attempt to synthesize alcohol of type **5** (Scheme 1) from **22** under Baylis–Hillman condition directly afford cross-conjugated α,β-unsaturated ester **3** in 63% yields (Scheme 4).



Scheme 4. Synthetic approach to ergot alkaloids.

Having cross-conjugated α,β-unsaturated ester **3** in hand, we then turned our attention for synthesis of tetracyclic core of ergot alkaloids either a 6-*endo-trig* cyclisation[20] of *s-cis* conformer **3** or a 6-*exo-trig* cyclisation of *s-trans* conformer **4**.

To our delight, upon treatment of **3** with HCOOH at RT, the reaction followed an *aza*-Michael reaction to afford **23** and **24** bearing the requisite functionalities in 2:1 d.r. in favor of **23**.[21] Thus, the final stage was set for the completion of the total synthesis of lysergol (**1 b**), and isolysergol (**1 d**) (Scheme 5). Towards this, $LiAlH_4$ reduction of mixture of **23** and **24** gave chromatographically separable diastereomers of **25** and **26**, respectively. Finally, deprotection of the *p*-Ts group of **25** and **26** using Mg/MeOH completed total syntheses of lysergol (**1 b**) and isolysergol (**1 d**), respectively.



Scheme 5. Total syntheses of lysergol (**1 b**) and isolysergol (**1 d**).

In conclusion, we developed a novel entry to direct construction of an ergot alkaloid skeleton based on a 6-*endo-trig* cyclisation of a cross-conjugated α,β-unsaturated ester. This was achieved by means of an enantioselective thiourea-catalyzed intramolecular Michael reaction of nitronate onto α,β-unsaturated ester in 97% *ee*. Utilizing this methodology, we have shown first total syntheses of ergot alkaloids, festuclavine (**1 c**), and pyroclavine (**1 e**) as well as unified total syntheses of other congeners, such as lysergol (**1 b**), and isolysergol (**1 d**). Further application of intramolecular Michael reaction for total synthesis of other complex alkaloids are under active investigations.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: *6-endo-trig* cyclisation · alkaloids · Michael reaction · synthetic methods · total synthesis

[1] a) C. L. Schardl, D. G. Panaccione, P. Tudzynski, in *The Alkaloids, Vol. 63* (Ed.: G. A. Cordell), Academic Press, San Diego, **2006**, pp. 45–86; b) M. Somei, Y. Yokoyama, Y. Murakami, I. Ninomiya, T. Kiguchi, T. Naito, In *The Alkaloids* (Ed: G. A. Cordell), Academic Press, San Diego, **2000**, *Vol. 54*, pp. 191–257.

[2] a) H. G. Floss, *Tetrahedron* **1976**, *32*, 873; b) D. D. Schwarzer, P. J. Gritsch, T. Gaich, *Synlett* **2013**, *24*, 1025–1031; c) C. Wallwey, S.-M. Li, *Nat. Prod. Rep.* **2011**, *28*, 496.

[3] a) E. C. Kornfeld, E. J. Fornefeld, G. B. Kline, M. J. Mann, D. Morrison, R. G. Jones, R. B. Woodward, *J. Am. Chem. Soc.* **1956**, *78*, 3087; b) W, Oppolzer, E. Francotte, K. Battig, *Helv. Chim. Acta* **1981**, *64*, 478; c) J. Rebek, D. F. Tai, Y.-K. Shue, *J. Am. Chem. Soc.* **1984**, *106*, 1813; d) C. Saá, D. D. Crotts, G. Hsu, K. P. C. Vollhardt, *Synlett* **1994**, 487; e) J. B. Hendrickson, J. Wang, *Org. Lett.* **2004**, *6*, 3; f) I. Moldvai, E. Temesvári-Major, M. Incze, É.

Szentirmay, E. Gács-Baitz, C. J. Szántay, *Org. Chem.* **2004**, *69*, 5993; g) S. Inuki, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2008**, *10*, 5239; h) S. Inuki, A. Iwata, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2011**, *76*, 2072; i) S. Inuki, S. Oishi, N. Fujii, H. Ohno, *Org. Lett.* **2011**, *13*, 2145; j) A. Iwata, S. Inuki, S. Oishi, N. Fujii, H. Ohno, *J. Org. Chem.* **2011**, *76*, 5506; k) Q. Liu, Y. Jia, *Org. Lett.* **2011**, *13*, 4810; l) S. Umezaki, S. Yokoshima, T. Fukuyama, *Org. Lett.* **2013**, *15*, 4230; m) H. Yuan, Z. Guo, T. Luo, *Org. Lett.* **2017**, *19*, 624; n) B. Milde, M. Pawliczek, P. G. Jones, D. B. Werz, *Org. Lett.* **2017**, *19*, 1914 and references therein.

[4] a) I.-K. Park, J. Park, C.-G. Cho, *Angew. Chem. Int. Ed.* **2012**, *51*, 2496; *Angew. Chem.* **2012**, *124*, 2546; b) D. Shan, Y. Gao, Y. Jia, *Angew. Chem. Int. Ed.* **2013**, *52*, 4902; *Angew. Chem.* **2013**, *125*, 5002; c) S. P. Breazzano, Y. B. Poudel, D. L. Boger, *J. Am. Chem. Soc.* **2013**, *135*, 1600; d) V. Lanke, K. R. Prabhu, *Org. Lett.* **2013**, *15*, 6262; e) T. Piou, A. Bunescu, Q. Wang, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.* **2013**, *52*, 12385; *Angew. Chem.* **2013**, *125*, 12611; f) T. Miura, Y. Funakoshi, M. Murakami, *J. Am. Chem. Soc.* **2014**, *136*, 2272.

[5] a) For a racemic approach to ergot alkaloids via Micheal reaction of nitronate, see; M. Somei, F. Yamada, H. Ohnishi, Y. Makita, M. Kuriki, *Heterocycles* **1987**, *26*, 2823; b) For an enantioselective approach using chiral phosphoric acid, see; S. Romanini, E. Galletti, L. Caruana, A. Mazzanti, F. Himo, S. Santoro, M. Fochi, L. Bernardi, *Chem. Eur. J.* **2015**, *21*, 17578.

[6] a) W. J. Nodes, D. R. Nutt, A. M. Chippindale, A. J. A. Cobb, *J. Am. Chem. Soc.* **2009**, *131*, 16016; b) Z.-X. Jia, Y.-C. Luo, X.-N. Cheng, P.-F. Xu, Y.-C. Gu, *J. Org. Chem.* **2013**, *78*, 6488; c) For an intermolecular version, see; S. Rajkumar, K. Shankland, G. D. Brown, A. J. A. Cobb, *Chem. Sci.* **2012**, *3*, 584.

[7] P. Perlmutter, *Conjugate Addition Reactions in Organic Synthesis*, Pergamon Press, Oxford, **1992**.

[8] For selected reviews, see: a) T. Ooi, K. Maruoka, *Acc. Chem. Res.* **2004**, *37*, 526; b) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580; c) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. Mcdaid, L. Deng, *Acc. Chem. Res.* **2004**, *37*, 621; d) P. I. Dalko, L. Moisan, *Angew. Chem. Int. Ed.* **2004**, *43*, 5138; *Angew. Chem.* **2004**, *116*, 5248; e) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701; f) D. Almasi, D. A. Alonso, C. Nájera, *Tetrahedron: Asymmetry* **2007**, *18*, 299.

[9] For selected examples: a) Y. K. Chen, M. Yoshida, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2006**, *128*, 9328; b) H.-H. Lu, X.-F. Wang, C.-J. Yao, J.-M. Zhang, H. Wu, W.-J. Xiao, *Chem. Commun.* **2009**, 4251; c) C. Rabalakos, W. D. Wulff, *J. Am. Chem. Soc.* **2008**, *130*, 13524.

[10] Vinyl sulfones and phosphonates have recently emerged as Michael acceptors in organocatalytic processes. S. Sulzer-Mossé, A. Alexakis, J. Mareda, G. Bollot, G. Bernardinelli, Y. Filinchuk, *Chem. Eur. J.* **2009**, *15*, 3204.

[11] For examples, see: a) T. Marcelli, R. N. S. van der Haas, J. H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45*, 929; *Angew. Chem.* **2006**, *118*, 943; b) T. Okino, S. Nakamura, T. Furukawa, Y. Takemoto, *Org. Lett.* **2004**, *6*, 625. For recent reviews of bifunctional organocatalysts, see: c) S. J. Connon, *Chem. Commun.* **2008**, 2499; d) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520; *Angew. Chem.* **2006**, *118*, 1550.

[12] a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672; b) T. Okino, Y. Hoashi, T. Furukawa, X. Xu, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119; c) S. H. McCooey, S. J. Connon, *Angew. Chem. Int. Ed.* **2005**, *44*, 6367; *Angew. Chem.* **2005**, *117*, 6525; d) J. Ye, D. J. Dixon, P. S. Hynes, *Chem. Commun.* **2005**, 4481; e) B. Vakulya, S. Varga, A. Csámpai, T. Soós, *Org. Lett.* **2005**, *7*, 1967.

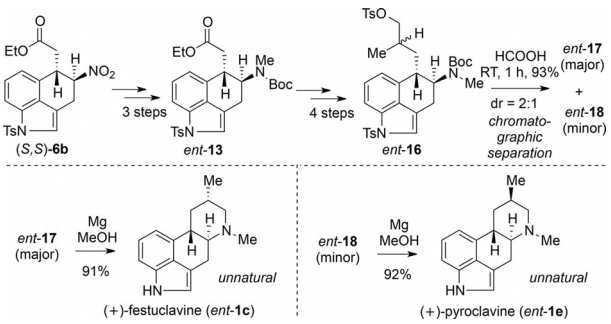
[13] J. P. Malerich, K. Hagihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416.

[14] Representative computational work on the bifunctional thiourea organocatalysis, see: a) A. Hamza, G. Schubert, T. Soós, I. Pápai, *J. Am. Chem. Soc.* **2006**, *128*, 13151; b) J.-L. Zhu, Y. Zhang, C. Liu, A.-M. Zheng, W. Wang, *J. Org. Chem.* **2012**, *77*, 9813; c) B. Kótai, G. Kardos, A. Hamza, V. Farkas, I. Pápai, T. Soós, *Chem. Eur. J.* **2014**, *20*, 5631; d) M. N. Grayson, K. N. Houk, *J. Am. Chem. Soc.* **2016**, *138*, 9041 and references therein.

[15] For synthetic studies on Z-ester, please see the Supporting Information.

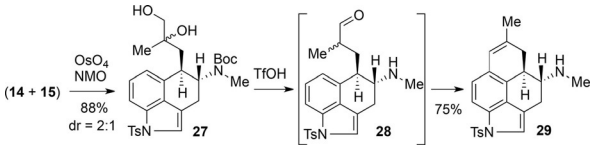
[16] The *syn*-stereochemistry of minor product (*S*,*R*)-**6a** was confirmed by nOe experiment (See, SI for details). Interestingly, minor product (*S*,*R*)-**6a** can be converted to (*S*,*S*)-**6a** in 72% yield by epimerization in the presence of 6 equiv of Et_3N in refluxing toluene, thereby increasing overall efficiency of our strategy.

[17] Absolute stereochemistry of major diastereomer (*S*,*S*)-**6b** was established by total synthesis of unnatural (+)-festuclavine (*ent*-**1c**) and (+)-pyroclavine (*ent*-**1e**) (please see Scheme below).



[18] Catalytic intramolecular Michael reaction of compound **11b** (1 g scale) using 5 mol% thiourea catalyst **L3** afforded (*R*,*R*)-**6b** in 85% yield (≈7 d) with 97% *ee* (d.r. = 3.6:1).

[19] Aldehyde **28** could be an advanced intermediate for the synthesis of ergot alkaloids via a reductive cyclization. However, an attempt towards this from diol **27** lead to the formation of unexpected tetracyclic compound **29** in 75% yield as sole product (See Supporting Information for plausible mechanism).



[20] For synthesis of pancratistatin analogues using 6-*endo*-*trig* cyclisation, see; G. Pandey, M. Balakrishnan, *J. Org. Chem.* **2008**, *73*, 8128.

[21] Diastereomeric mixture of methylester analogue of **23** and **24** is known to produce lysergic acid via one pot saponification and tosyl deprotection reflux condition, for reference see 3 L.

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