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Communication

Enantioselective Total Synthesis of (+)-Stephadiamine through Bioinspired Aza-Benzilic Acid Type Rearrangement

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ABSTRACT: We report the first enantioselective total syntheses of the hasubanan alkaloid (−)-metaphanine and the norhasubanan alkaloid (+)-stephadiamine. Key features of these syntheses include diastereoselective oxidative phenolic coupling reaction and subsequent regioselective intramolecular aza-Michael reaction, which efficiently construct the hasubanan skeleton with the all-carbon quaternary stereogenic center at C13. Based on our hypothesis regarding the biosynthetic pathway of (+)-stephadiamine, we found that (−)-metaphanine is easily converted to (+)-stephadiamine via aza-benzilic acid type rearrangement reaction.

Plants of the genus *Stephania*, which grow naturally in the Southeast Asia-Pacific region and have been widely used in traditional Chinese medicines, contain bioactive alkaloids known as hasubanans.[1] More than 40 congeners of these alkaloids have been identified to date, and they show a wide range of biological activities, including antiviral, antimicrobial, and cytotoxic activities.[1c] Hasubanan alkaloids, exemplified by compounds **2**−**5**, commonly possess a characteristic tetracyclic aza[4,4,3]propellane core **1** (Figure 1a).[1,2] Owing to the synthetically challenging structures of these alkaloids as well as their important biological activities, numerous synthetic studies have been reported.[3−5]

In 1984, Ibuka and co-workers isolated a (+)-stephadiamine (**6**) from *Stephania japonica*.[6] This norhasubanan alkaloid has an uncommon structure that differs from those of hasubanan alkaloids. It contains an aza[4,3,3]propellane scaffold with a five-membered C-ring, and four stereogenic centers, including an α-tertiary amine at C14 and an all-carbon quaternary stereogenic center at C13. The unique caged-type structure of **6** and its absolute configuration were established by X-ray crystallography analysis of the bromobenzoate derivative. The biological activity of **6** has not yet been investigated, because only a limited supply is available from nature. Furthermore, despite the interesting structure of **6**, only one report of its total synthesis has appeared to date. In 2018, Trauner and co-workers reported a total synthesis of stephadiamine (**6**) in racemic form based upon an elegant cascade reaction of a β-tetralone derivative for the construction of the characteristic aza[4,3,3]propellane core, which corresponds to the B,C,D-rings in **6**.[7] As a part of their synthesis, they described enantioselective access to a key intermediate by means of Pd-catalyzed asymmetric allylation with chiral phosphoric acid.

The biosynthetic pathway of the hasubanan alkaloids has been explored in part, although it is still not fully established.[8] We envisaged that the five-membered C-ring of the norhasubanan **6** might be formed biosynthetically from the six-membered hasubanan C-ring, e.g., by reconstruction of the hemiacetal in **5** to δ-lactone (Figure 1b). That is, we hypothesized that (+)-stephadiamine (**6**) would be formed biosynthetically from (−)-metaphanine (**5**) through an aza-benzilic acid type rearrangement reaction via intermediate **7**, which would be generated by condensation of **5** with ammonia.[9] Based on this hypothesis, we considered that this aza-benzilic acid-type rearrangement might be applied to synthesize (+)-stephadiamine (**6**) from its putative biosynthetic precursor, (−)-metaphanine (**5**). In this report, we describe enantioselective total syntheses of (−)-metaphanine (**5**) and (+)-stephadiamine (**6**), featuring a diastereoselective oxidative phenolic coupling reaction and subsequent regioselective intramolecular aza-Michael reaction, as well as the bioinspired aza-benzilic acid type rearrangement.

Our synthetic analysis for the primary target, (−)-metaphanine (**5**), is depicted in Figure 1c. We envisaged that **5** would be obtained by selective oxidation at C8 in enone **8**, which would be synthesized by successive construction of the B and D rings through a diastereoselective oxidative phenolic coupling reaction of phenol **10**, followed by regioselective intramolecular aza-Michael reaction of the resulting dienone **9**. In the synthesis of the B ring in **9**, the stereochemistry at C13 with the all-carbon quaternary stereogenic center was expected to be controlled by C10 in **10**. According to this synthetic plan, all of the stereochemistry in the hasubanan skeleton would be controlled by the stereocenter at C10. We planned to synthesize phenol **10** by coupling of **11** and **12**, which correspond to the A- and C-rings in **5**, respectively.

Our synthesis commenced with the construction of the stereocenter at C10 in (−)-metaphanine (**5**) (Scheme 1). First, the coupling reaction of TMS cyanohydrin **11** and mesylate **12**,[10] which correspond to the A- and C-rings, respectively, was carried out with LiHMDS followed by

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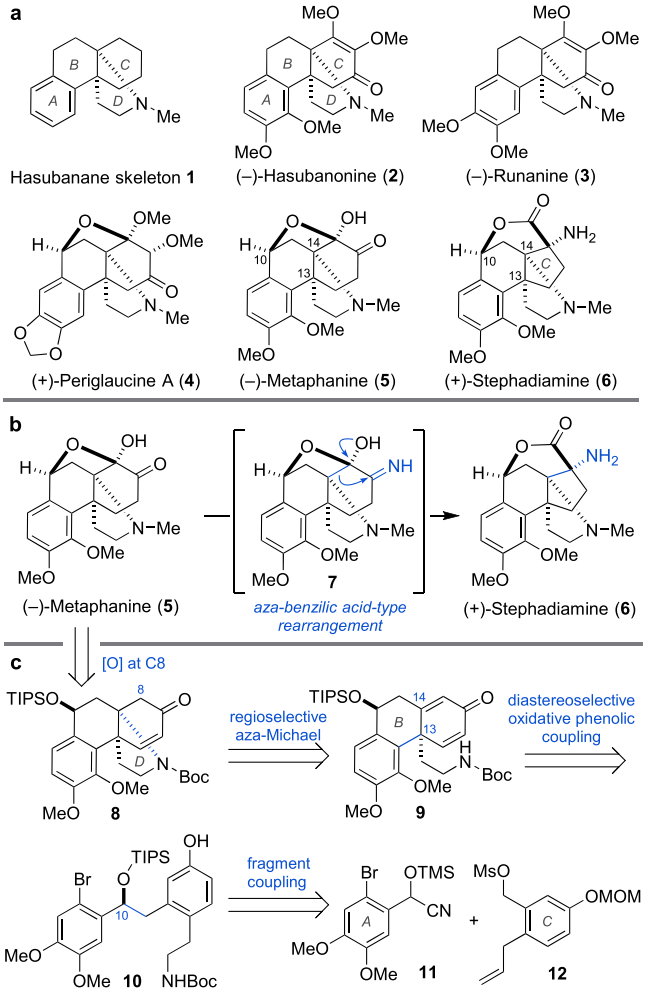

Figure 1. (a) Structures of representative hasubanan alkaloids. (b) Proposed biosynthetic pathway leading to stephadiamine (**6**) from **5**. (c) Retrosynthetic analysis of metaphanine (**5**) and stephadiamine (**6**).

treatment with TBAF to give **13** in 78% yield. We next investigated control of the stereochemistry at C10 of the ketone in **13** under various asymmetric reduction conditions, using CBS reduction[11] and Noyori's hydrogenation-transfer conditions,[12,13] but only moderate selectivity was obtained (see Supporting Information). Thus, we examined various acylative kinetic resolution (KR) conditions with racemic alcohol *rac*-**14**, obtained by reduction of **13** with sodium borohydride, using chiral isothiourea catalysts.[14] The desired alcohol (−)-**14** was obtained with excellent enantioselectivity (over 99% ee) by employing a catalytic amount of (2*S*,3*R*)-HyperBTM (**15**) in the presence of isobutyric anhydride as an acylating reagent.[15,16] Isobutyric ester **16** obtained in this process was recyclable to the ketone **13** almost quantitatively by removal of the acyl group under basic conditions, followed by oxidation of the resulting alcohol.

Then, we shifted our attention to the construction of the all-carbon quaternary stereogenic center at C13 by means of oxidative dearomative coupling reaction. The substrate phenol **20** for this conversion was synthesized as follows. Protection of the alcohol in (−)-**14** with silyl ether followed by ozonolysis and reduction of the allyl group gave alcohol **18**. The hydroxyl group in **18** was converted into azide by mesylation followed by treatment with sodium azide to give **19** in 72% yield. The azide group in **19** was then reduced to amine under the Staudinger conditions, and the resulting amine was protected with a Boc group, followed by deprotection of the MOM group with a catalytic amount of terabromomethane in 2-propanol to give phenol **20**.[17] With the phenol **20** in hand, oxidative dearomative phenolic coupling reaction was investigated.[18] Thus, phenol **20** was treated with PIDA in hexafluoro-2-propanol (HFIP) at 0 °C in the presence of methanol as an additive.[19] Under these conditions, the coupling reaction proceeded to afford the dienone **21** in 34% yield as a single diastereomer.[20] In this reaction, two possible transition states, **TS-1** and **TS-2**, can be considered regarding the configuration at C10, and the reaction would preferentially proceed from the sterically less hindered transition state **TS-1** to predominantly form **21** having the desired configuration at C13.

With the tricyclic hasubanan framework (A,B,C-rings) of **21** in place, construction of the D-ring was investigated by means of regioselective intramolecular aza-Michael reaction. After debromination of **21** with sodium formate in the presence of $Pd(PPh_3)_4$, the resulting dienone **9** was subjected to intramolecular aza-Michael reaction (Table 1). First, we examined the reaction with Brønsted acids (entries 1, 2). In the case of trifluoroacetic acid, the sterically less hindered C5 adduct **23** was obtained as the major product (**8**/**23** = 1:4.4 ratio). On the other hand, the adducts at C5 and C14, **23** and **8**, were obtained in 68% total yield with an approximately 1:1 ratio upon reaction with hydrochloric acid. Thus, we focused on basic conditions. In the case of DBU in THF at rt, no reaction took place, presumably due to the weak basicity, and the substrate **9** was recovered quantitatively (entry 3). Stronger bases such as sodium hydride or sodium *tert*-butoxide gave mixtures of **8** and **23** in 67% and 60% yields, respectively, with no selectivity (entries 4, 5). Interestingly, tetracyclic C14 adduct **8** was obtained predominantly (**8**/**23** = 1.9:1 ratio) in 59% yield with potassium *tert*-butoxide in THF at 0 °C, and the selectivity was drastically increased to 7.3:1 (**8**/**23**) in a mixed solvent system (THF/HMPA = 9:1) at 0 °C. The desired **8** was obtained in 51% yield after separation on a silica gel column (entry 7).

With tetracyclic **8** in hand, we moved on to the syntheses of (−)-metaphanine (**5**) and (+)-stephadiamine (**6**) (Scheme 2). First, we examined selective oxidation at C8 of enone **8**. After several attempts, we found that the Davis oxaziridine oxidant *rac*-**24** was effective, affording α-hydroxy ketone **25** in 71% yield. After oxidation of the hydroxyl group with DMP in **25**, the TIPS ether in the resulting **26** was deprotected with HF·Et_3N to give the hemiacetal **27** in 77% yield from **25**. Then, the double bond in **27** was reduced under hydrogenation conditions to give **28** in 80% yield. Finally, (−)-metaphanine (**5**) was synthesized from **28** by deprotection of the Boc group with hydrochloric acid followed by reductive methylation of the resulting amine with formaldehyde and cyanoborohydride in 45% yield. The structure of the synthetic (−)-metaphanine (**5**) was confirmed by X-ray crystallography analysis and comparison of the spectral data of ^{1}H and ^{13}C NMR with previously reported values.[21,22]

As already mentioned, we had hypothesized that stephadiamine (**6**) would be biosynthetically generated from metaphanine (**5**). To test this idea, we examined the transformation of (−)-metaphanine (**5**) into (+)-stephadiamine (**6**). As we had hoped, aza-benzilic acid type rearrangement proceeded upon treatment of **5** with ammonia

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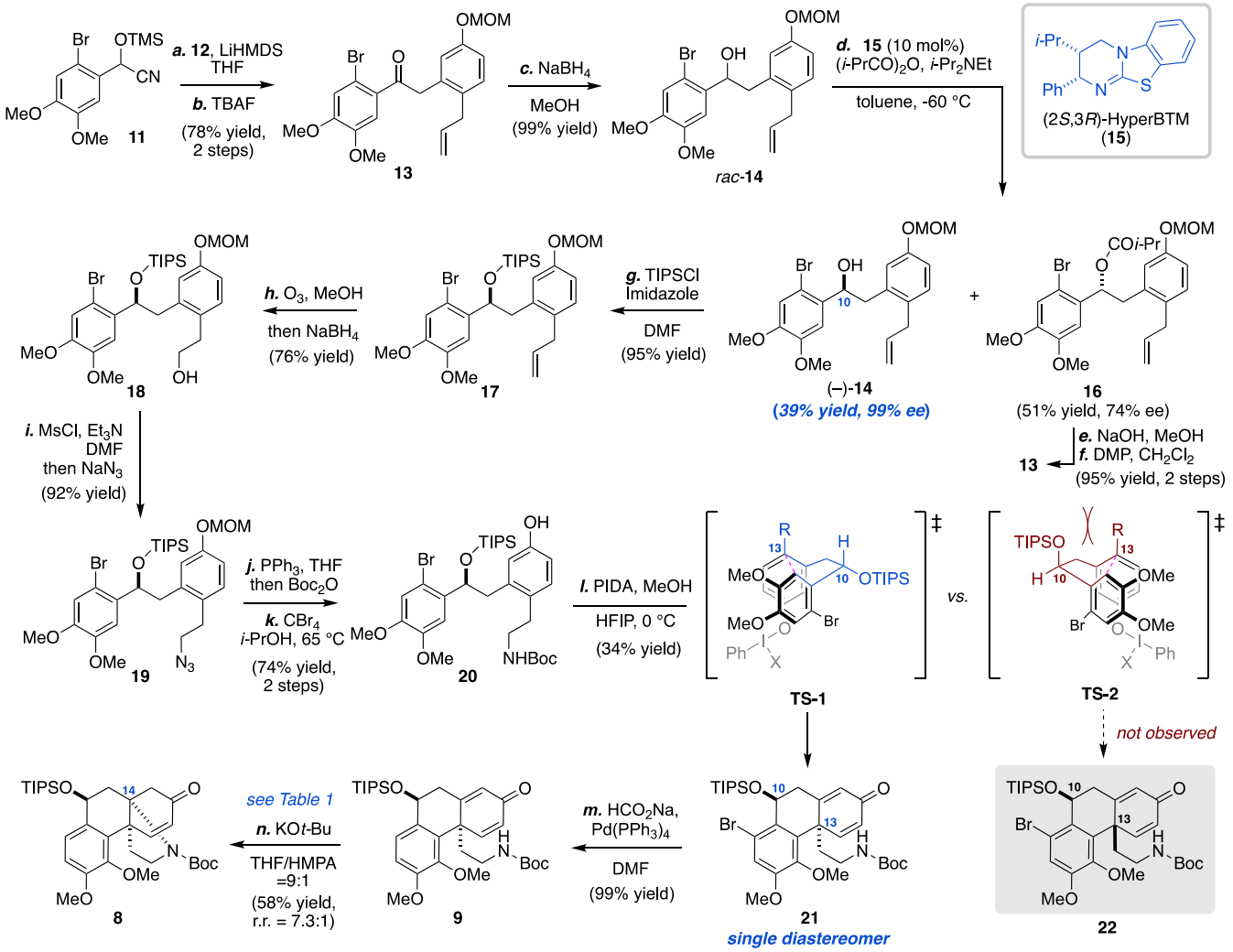
Scheme 1. Synthesis of Pivotal Intermediate 8[a]



[a]Reagents and conditions: (a) **12** (1.0 equiv), LiHMDS (1.3 equiv), THF, −78 to 0 °C, 45 min; (b) TBAF (1.0 equiv), THF, 0 °C, 5 min (78%, 2 steps); (c) $NaBH_4$ (1.5 equiv), MeOH, 0 °C, 10 min (99%); (d) **15** (10 mol %), $(i\text{-PrCO})_2O$ (0.6 equiv), $i\text{-Pr}_2NEt$ (0.6 equiv), toluene, −60 °C, 8 h ((−)-**14**, 39%, 99% ee), (**16**, 51%, 74% ee); (e) NaOH (12 equiv), MeOH, rt, 10 min; (f) DMP (1.5 equiv), CH_2Cl_2, rt, 1 h (95%, 2 steps); (g) TIPSCl (2.0 equiv), imidazole (4.0 equiv), DMF, 65 °C, 12 h (95%); (h) O_3 (gas), MeOH, −78 °C, 5 min, then $NaBH_4$ (3.0 equiv), 0 °C, 30 min (76%); (i) MsCl (1.2 equiv), Et_3N (1.5 equiv), DMF, 0 °C, 10 min, then NaN_3 (2.0 equiv), 65 °C, 6 h (92%); (j) PPh_3 (2.0 equiv), H_2O (10.0 equiv), THF, 65 °C, 6 h, then Boc_2O (2.0 equiv), rt, 1 h; (k) CBr_4 (0.2 equiv), *i*-PrOH, 65 °C, 3 h (74%, 2 steps); (l) PIDA (1.0 equiv), MeOH (100 equiv), HFIP, 0 °C, 5 min (34%), (m) HCO_2Na (1.5 equiv), $Pd(PPh_3)_4$ (10 mol %), DMF, 100 °C, 2 h (99% yield); (n) KO*t*-Bu (5.0 equiv), THF/HMPA, 0 °C, 5 min (51%). LiHMDS = Lithium bis(trimethylsilyl)amide, THF = tetrahydrofuran, TBAF = tetra-*n*-butylammonium fluoride, DMP = Dess-Martin periodinane, DMF = *N*,*N*-dimethylformamide, MsCl = methanesulfonyl chloride, Boc_2O = di-*tert*-butyl dicarbonate, PIDA = iodobenzene diacetate, HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol, HMPA = hexamethylphosphoric triamide.

in methanol at room temperature, affording exclusively (+)-stephadiamine (**6**) via an imine intermediate **7**. Although purification was difficult because of the instability of **6** on an ODS or a silica gel column under acidic or basic conditions, as already reported,[6,7] we were able to obtain satisfactory analytical data, including ^1H and ^{13}C NMR spectra, for identification of the structure of **6** without purification of the reaction mixture.

In summary, we have achieved the first enantioselective total syntheses of (−)-metaphanine (**5**) and (+)-stephadiamine (**6**). Based on our hypothesis that (+)-stephadiamine (**6**) would be formed biosynthetically from (−)-metaphanine (**5**), we investigated this bioinspired aza-benzilic acid-type rearrangement and excitingly found that the reaction proceeds as expected simply upon treatment with ammonia. The present syntheses also feature diastereoselective oxidative phenolic coupling and subsequent regioselective intramolecular aza-Michael reaction for the construction of the hasubanan skeleton of (−)-metaphanine (**5**), and this strategy is expected to provide access to a variety of hasubanan alkaloids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c00047.

Experimental Procedures, spectroscopic date for all compounds, and HPLC analysis (PDF)

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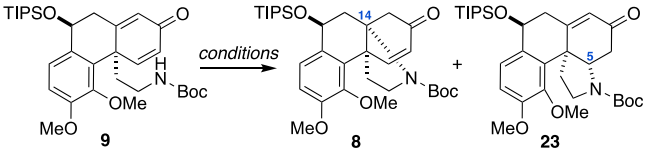
Table 1. Investigation of Regioselective Aza-Michael Reaction with Dienone 9



entry	conditions	8 and 23 yield (%)[a]	ratio (8:23)[b]
1	TFA,[c] CH_2Cl_2, 0 °C to rt.	66	1:4.4
2	HCl/1,4-dioxane,[c] CH_2Cl_2, 0 °C	68	1.2:1
3	DBU,[d] THF, 0 °C to rt	no reaction	
4	NaH,[d] THF, 0 °C	67	1:1.2
5	NaO*t*-Bu,[d] THF, 0 °C	60	1:1
6	KO*t*-Bu,[d] THF, 0 °C	59	1.9:1
7	KO*t*-Bu,[d] THF/HMPA (9:1), 0 °C	58 (51)[e]	7.3:1

[a]Total yield of **8** and **23**. [b]Determined from the ^{1}H NMR spectrum of the crude material, [c]1.0 equiv. [d]5.0 equiv. [e]Isolated yield of **8**.

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Notes

The authors declare no competing financial interest.

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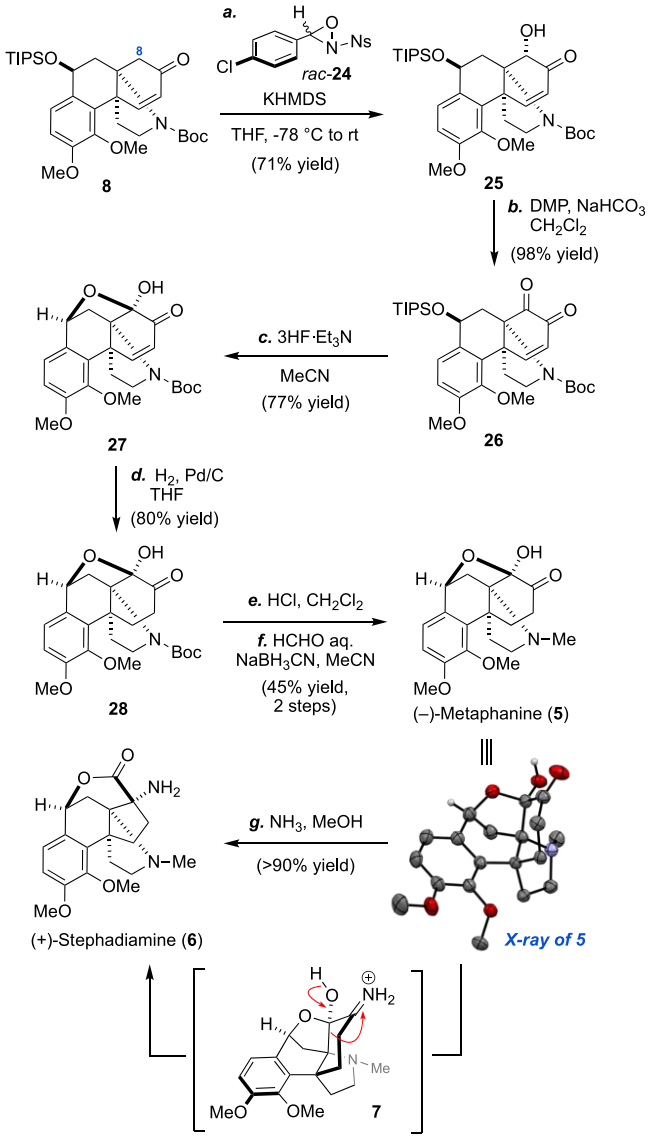
Scheme 2. Completion of the Syntheses of Metaphanine (5) and Stephadiamine (6)[a]



[a]Reagents and conditions: (a) *rac*-**24** (2.0 equiv), KHMDS (3.0 equiv), THF, −78 °C to rt, 6 h (71%); (b) DMP (3.0 equiv), $NaHCO_3$ (6.0 equiv), CH_2Cl_2, rt, 3 h (98%); (c) 3HF·Et_3N (50 equiv), MeCN, rt, 6 h (77%); (d) H_2 (balloon), Pd/C (10 wt %), THF, rt, 30 min (80%); (e) HCl (4 M in 1,4-dioxane, 100 equiv), CH_2Cl_2, 0 °C to rt, 30 min; (f) HCHO (12.3 M in H_2O, 3.0 equiv), $NaBH_3CN$ (1.5 equiv), MeCN, 0 °C, 30 min (45%, 2 steps); (g) NH_3 (2 M in MeOH, 200 equiv), rt, 6 h (>90%).

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