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Synthesis and evaluation of 1,1,7,7-tetramethyl-9-azajulolidine (TMAJ) as a highly active derivative of *N*,*N*-dimethylaminopyridine

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ABSTRACT

1,1,7,7-Tetramethyl-9-azajulolidine (TMAJ), which theoretical studies have suggested as a highly active DMAP analog, was synthesized for the first time. The catalytic activity of TMAJ was confirmed by the acetylation reactions of various *tert*-alcohols. TMAJ showed much higher catalytic activity than DMAP and one of the highest activity levels among the conventional DMAP analogs. These experimental results were in good agreement with the previous theoretical studies.

N,*N*-Dimethylaminopyridine (DMAP) is one of the most widely used organocatalysts in the field of organic chemistry.[1] In particular, DMAP is the most common catalyst for condensation reactions of various alcohols, amines, and so on. Thus, the development of more active derivatives of DMAP has been a subject of intensive research.[2] The catalytic activity of DMAP analogs tends to increase with the electron-donating properties of the 4-substituent, and 4-pyrolidinopyridine (PPY) has been used as a more reactive analog than DMAP.[3] In 2003, Steglich *et al.* reported that bis-six-membered DMAP analog 9-azajulolidine (9-AJ), synthesized according to Yamanaka's procedure,[4] showed about six times the catalytic activity of DMAP in the esterification reaction of a tertiary alcohol.[5] After that report, Han's group improved the synthesis of 9-AJ[6] and developed an aza-analog that is slightly better than 9-AJ.[7] Wong's group also reported the improved synthesis of 9-AJ and its application to the post-Ullmann reaction.[8] Moreover, various aza-analogs of 9-AJ were developed as highly nucleophilic pyridines.[9] In these ways, cyclic analogs of DMAP have been intensively studied. Among them, the bis-six-membered analogs have exhibited the highest catalytic activity so far. On the other hand, Zipse *et al.* vigorously investigated the catalytically most active DMAP derivatives by computational studies.[10] They reported that 1,1,7,7-tetramethyl-9-azajulolidine **1** (TMAJ), the tetramethylated analog of 9-AJ, forms the most stable acylpyridinium cation intermediate next to the Fu's ferrocene analog[11] in various DMAP analogs.[10a] However, although various derivatives of 9-AJ have been developed so far, TMAJ (**1**), which was suggested to be the most efficient DMAP analog, has not yet been synthesized. The main reason for this is probably the difficulty of synthesizing **1**. In particular, the introduction of quaternary carbon centers to the neighboring position of the pyridine ring is generally difficult. For example, the Friedel-Crafts-type reaction is not suitable for the pyridine ring because pyridine is an electron-deficient aromatic ring. The intramolecular radical cyclization reactions and the Heck reactions were likely to preferentially proceed with 5-*exo* cyclizations. On the other hand, we recently reported the concise synthesis of quinolizidine alkaloid (+)-epilupinine.[12] As **1** also includes the quinolizidine skeleton, we considered that our synthetic method for quinolizidine alkaloids can be applied to the synthesis of **1**. Herein, we report the first synthesis of TMAJ (**1**) and assess its ability as an acylation catalyst.

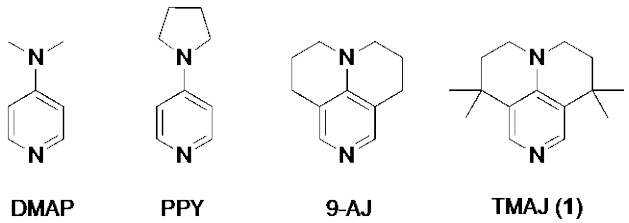

Figure 1. Structures of DMAP analogs

Our synthesis of (+)-epilupinine was achieved by the cascade reaction of **2**. Treatment of **2** with PhSH and L-proline induced sequential reactions consisted of a removal of nosyl group, condensation of the resulting secondary amine with either

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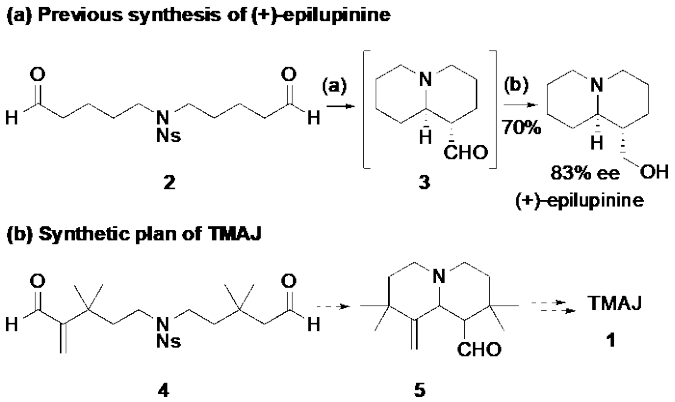
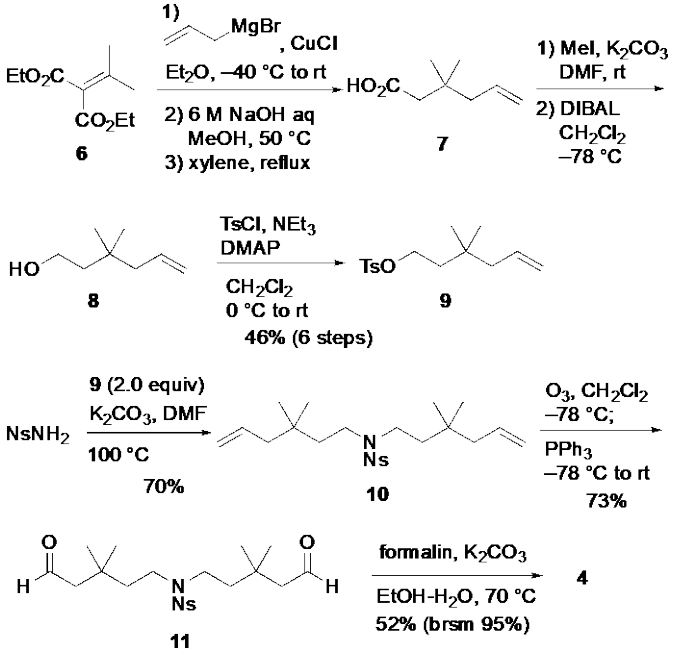
aldehyde, and an intramolecular asymmetric Mannich reaction to give **3**. Subsequent direct addition of $NaBH_4$ and methanol to the reaction mixture afforded (+)-epilupinine in one step from **2** (Scheme 1a). Based on this quinolizidine-forming reaction, we designed **4** possessing tetramethyl groups and exomethylene moiety as the precursor of a similar cascade reaction that would afford quinolizidine compound **5**. The pyridine formation using aldehyde and exomethylene moiety as a foothold would afford TMAJ (**1**) (Scheme 1b).



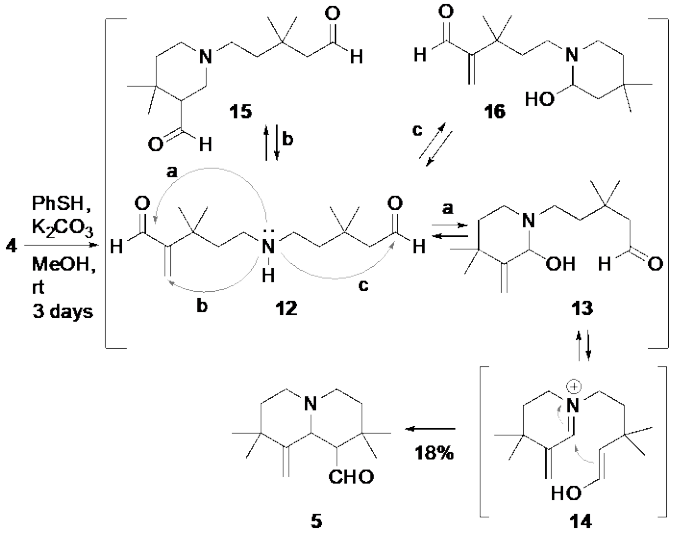
Scheme 1. Synthesis of (+)-epilupinine and synthetic plan of **1**. Reaction conditions; (a) PhSH, L-proline, Cs_2CO_3, $CHCl_3$, 0 °C. (b) $NaBH_4$, MeOH, 0 °C to rt.

We synthesized the cascade reaction precursor **4**. Starting with commercially available **6**, the conjugate addition of the allyl group followed by hydrolysis and decarboxylation afforded carboxylic acid **7**. The carboxylic acid moiety was reduced to alcohol **8**, and the resulting hydroxy group was converted into the tosylate group as a leaving group to give **9**. Next, commercially available *o*-nosylamide was treated with 2.0 equiv of **9** as an alkylating reagent to afford double-alkylated product **10** in 70% yield. After ozonolysis of **10**, treatment of the resulting dialdehyde **11** with 1.0 equiv of formalin under basic conditions afforded the desired cascade reaction precursor **4** (Scheme 2).



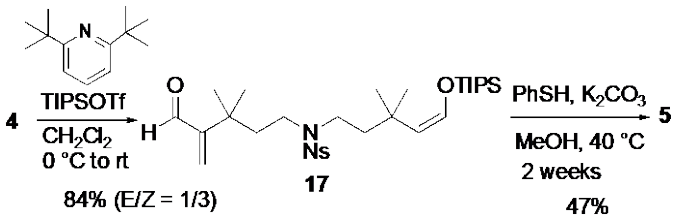
Scheme 2. Synthesis of the cascade reaction precursor **4**.

Having prepared the cascade reaction precursor, we tried the cascade reaction of **4**. Treatment of **4** with PhSH and K_2CO_3 in methanol for the removal of the nosyl group initially afforded reactive secondary amine **12**. Then, when the reaction was extended for a long time, the desired **5** gradually appeared as a single diastereomer.[13] The reaction leading to **5** probably consisted of the hemiaminal formation with the aldehyde on the enal side (**12**→**13**) and the generation of iminium cation (**13**→**14**) followed by the intramolecular Mannich reaction (**14**→**5**). Although the desired quinolizidine skeleton **5** was obtained in this cascade reaction, the yield of **5** had to be improved for further conversion. The main reason for the low yield and long reaction time is that the 1,4-addition reaction leading to **15** (path b) and the other hemiaminal formation leading to **16** (path c) compete with the desired hemiaminal formation, and these undesired reactions take precedence over the desired path a (Scheme 3). The reaction mainly afforded **15** and **16** at the beginning, and then **5** was gradually obtained through equilibrium.[14] Thus, we needed to suppress the undesired paths b and c to increase the yield of **5**.



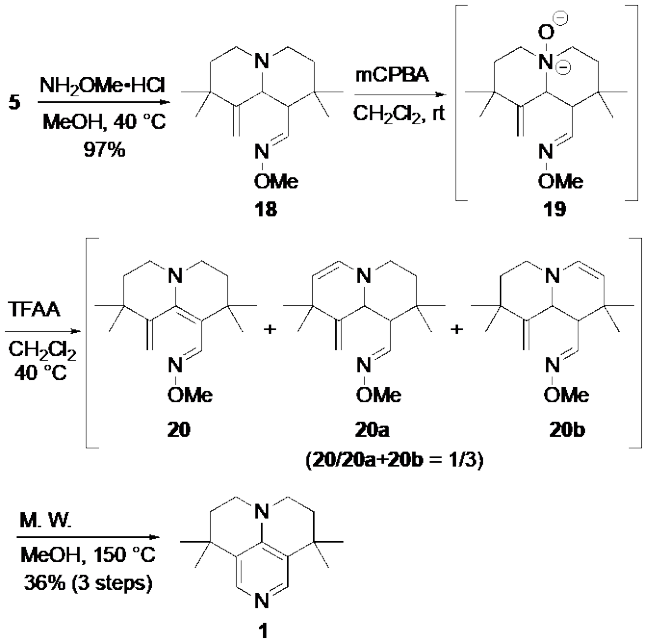
Scheme 3. The reaction pathway of the cascade reaction leading to **5**.

It was difficult to modify the olefin moiety to suppress path b despite our efforts. On the other hand, the unconjugated aldehyde was convertible into silyl enol ether **17** for the suppression of path c. A similar reaction of **17** increased the yield of **5** to 47%, although the reaction time was longer due to the unavoidable path b and the stability of TIPS enol ether. Indeed, it was confirmed that the 1,4-addition product was generated mainly in the early stage, and that the isolated 1,4-adduct was returned to enal under the reaction conditions. On the other hand, TBS enol ether instead of the TIPS group converted readily back to aldehyde before the removal of the nosyl group in the reaction conditions.



Scheme 4. Cascade reaction of silyl enol ether **17**.

With a sufficient amount of **5** in hand, we attempted the synthesis of TMAJ (**1**). Treatment of **5** with *O*-methylhydroxyamine afforded *O*-methyloxime **18** in excellent yield. We next applied the Polonovski reaction to introduce another double bond into **18**.[15] The tertiary amine of **18** was oxidized by *m*CPBA to give *N*-oxide **19**. Subsequent treatment of crude **19** with trifluoroacetic anhydride afforded the desired enamine **20**, along with inseparable regioisomers **20a** and **20b**. Although the desired **20** was a minor product, it was considered that major regioisomers **20a** and **20b** could also be isomerized to the desired isomer **20**.[16] Therefore, a mixture of the three isomers was heated to 150 °C by microwave irradiation, and the desired TMAJ (**1**) was obtained in 36% yield from **18**.



Scheme 5. Synthesis of TMAJ (**1**)

Having established the synthesis of **1**, we evaluated its catalytic activity. The acetylation reaction of unreactive tertiary alcohol **21** with acetic anhydride was adopted for the activity test according to the conventional evaluation of DMAP analogs. The progress of the reaction in the presence of 10 mol % of DMAP analogs as catalysts was observed by ^{1}H NMR spectroscopy. The yields of acetate **22** were plotted over a time course as shown in Figure 2. In comparison with DMAP and PPY, bis-six-membered analogs showed much higher catalytic activity. In particular, TMAJ (**1**) had the highest catalytic activity, ca. 1.5 times higher than 9-AJ.[5,17] These experimental results supported the theoretical studies reported by Zipse *et al.*[10a]

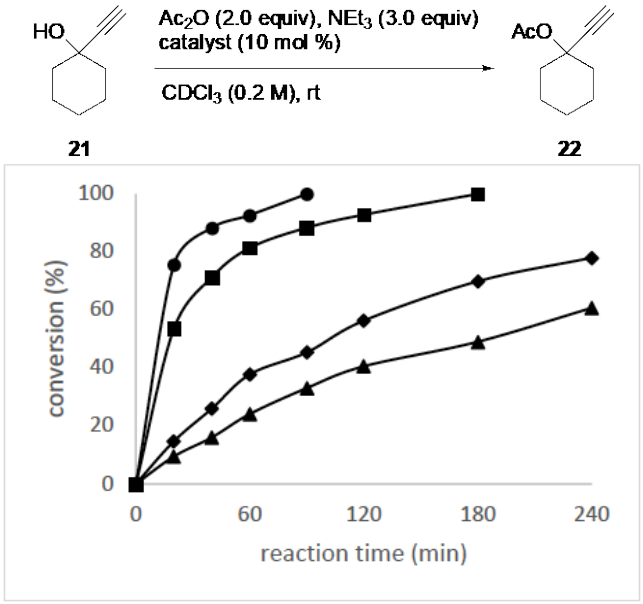
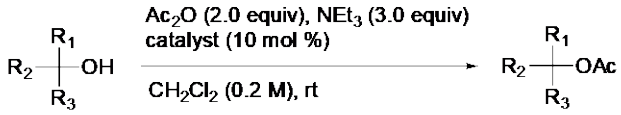
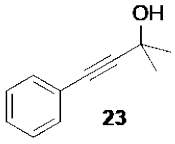
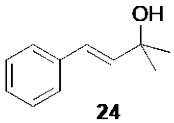
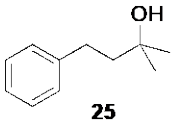
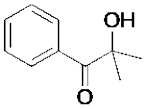
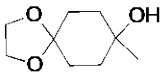
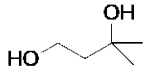


Figure 2. Time course of yield in the acetylation reaction of **21** using 10 mol % of DMAP analog catalyst: DMAP (▲), PPY (◆), 9-AJ (■), and TMAJ (●).

Finally, the acetylation reactions of various *tert*-alcohols using TMAJ as a catalyst were examined (Table 1). The reaction of aliphatic alkynyl alcohol **23** proceeded smoothly to give the desired acetate in 83% yield, while the use of DMAP significantly decreased the yield (entry 1). The reactions of alkenyl alcohol **24** and alkyl alcohol **25** also smoothly catalyzed by TMAJ (**1**) (entries 2 and 3). The reaction time was prolonged in the order of alkyl, alkenyl, and alkynyl group, reflecting the steric hindrance of these substituents. The reaction of *tert*-alcohol at the α-position of ketone **26** also gave the acetate in good yield, i.e., TMAJ accelerated the reaction in the *tert*-alcohol possessing strong electron with-drawing groups (entry 4). The case of cyclic trialkyl *tert*-alcohol **27** similarly gave the desired acetates in much higher yields than DMAP (entry 5). In addition, the reaction of diol **28** with 4.0 equiv of acetic anhydride afforded the corresponding diacetate in good yield (entry 6). Throughout, TMAJ (**1**) showed much higher catalytic activity than DMAP.

Table 1. Comparison of DMAP and TMAJ in reactions of various *tert*-alcohols.



entry	substrate	time (h)	yield (%)[a] DMAP	yield (%)[a] TMAJ
1	 **23**	1.3	46	83
2	 **24**	7.0	51	84
3	 **25**	11	51	84
4	 **26**	0.5	42	85
5[b]	 **27**	33	54	85
6[b]	 **28**	8	26	82

[a]NMR yield using pyrazine as an internal standard. [b]4.0 equiv of Ac_2O and 6.0 equiv of NEt_3 were used.

In conclusion, we achieved the first synthesis of TMAJ (**1**), which has been proposed as a highly active DMAP analog in theoretical studies. The catalytic activity of **1** was actually confirmed by the acetylation reaction of various *tert*-alcohols, and **1** showed much higher catalytic activity than DMAP and one of the highest activity levels among the conventional DMAP analogs. These experimental results were in good agreement with the previous theoretical studies. TMAJ (**1**) is expected to be widely used as an efficient catalyst for acylation reactions and various other reactions such as carbamylation, silylation,

sulfonylation, lactonization, and so on. For this purpose, the synthesis of **1** still needs several improvements regarding the number of steps, the yields, and the reaction time of the cascade reaction. In addition, chiral DMAP analogs have recently been developed and successfully applied to asymmetric syntheses.[18] Our synthesis of **1** can be applied to the development of novel chiral DMAP analogs that possess chiral centers at the 1- and 7-positions instead of a dimethyl group. Although the cascade reaction needs dimethyl groups so far, we are currently undertaking the improvement of the cascade reaction so that the reaction can be applied not only to the large-scale synthesis of TMAJ (**1**) but also to the development of novel chiral DMAP analogs.

Acknowledgments

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References and notes

1. (a) W. Steglichi, G. Höfle, Angew. Chem. Int. Ed., 8 (1969) 981; (b) G. Höfle, W. Steglich, H. Vorbrüggen, Angew. Chem. Int. Ed., 17 (1978) 569–583.
2. (a) A. C. Spivey, S. Arseniyadis, Angew. Chem. Int. Ed., 43 (2004) 5436–5441; (b) P. H.-Y. Cheong, C. C. Legault, J. M. Um, N. Celebi-Ölcüm, K. N. Houk, Chem. Rev., 111, (2011) 5042–5173.
3. (a) W. Steglich, G. Höfle, Tetrahedron Lett., 54 (1970) 4727–4730; (b) A. Hassner, L. R. Krepski, V. Alexanian, Tetrahedron, 34 (1978) 2069–2076.
4. T. Sakamoto, N. Miura, Y. Kondo, H. Yamanaka, Chem. Pharm. Bull., 34 (1986) 2018–2023.
5. M. R. Heinrich, H. S. Klisa, H. Mayr, W. Steglich, H. Zipse, Angew. Chem. Int. Ed., 42 (2003) 4826–4828.
6. S. Singh, G. Das, O. V. Singh, H. Han, Tetrahedron Lett., 48 (2007) 1983–1986.
7. S. Singh, G. Das, O. V. Singh, H. Han, Org. Lett., 9 (2007) 401–404.
8. K.-T. Wong, S.-T. Ku, F.-W. Yen, Tetrahedron Lett., 48 (2007) 5051–5054.
9. N. D. Rycke, G. Berionni, F. Couty, H. Mayr, R. Goumont, O. R. P. David, Org. Lett., 13 (2011) 530–533; (b) R. Tandon, T. Unzner, T. A. Nigst, N. D. Rycke, P. Mayer, B. Wendt, O. R. P. David, H. Zipse, Chem. Eur. J., 19 (2013) 643–6442.
10. (a) I. Held, A. Villinger, H. Zipse, Synthesis, (2005) 1425–1430; (b) I. Held, S. Xu, H. Zipse, Synthesis, (2007) 1185–1196; (c) I. Held, E. Larionov, C. Bozler, F. Wagner, H. Zipse, Synthesis, (2009) 2267–2277; (d) E. Larionov, H. Zipse, WIREs Comput. Mol. Sci., 1 (2011) 601–619; (e) E. Larionov, F. Achrainer, J. Humin, H. Zipse, ChemCatChem, 4 (2012) 559–566; (f) R. Tandon, H. Zipse, Lewis Base Catalysis in Organic Synthesis 1 (2016) 119–144.
11. J. C. Ruble, G. C. Fu, J. Org. Chem., 61 (1996) 7230–7231.
12. T. Tsutsumi, S. Karanjit, A. Nakayama, K. Namba, Org. Lett., 21 (2019) 2620–2624.
13. The single diastereomer is probably due to the epimerization of aldehyde to more stable isomer as is the case of (+)-epilupinine synthesis.
14. Although the yield of **5** was only 18%, other byproducts were not isolated. The reactive **12** readily induced the intermolecular reaction to give complex polymerized mixtures during the equilibrium even under diluted conditions. Indeed, the desired **5** was not obtained under the undiluted condition.
15. (a) M. J. Polonovski, M. Polonovski, Bull. Soc. Chim. Fr., 41 (1927) 1927–1208; (b) J. Zhang, Y.-Q. Wang, X.-W. Wang, W.-D. Z. Li, J. Org. Chem., 78 (2013) 6154–6162.
16. Similar isomerization in the Polonovski reaction, see: D. Grierson, Org. React., 39 (1990) 85–295.
17. The catalytic activity of **1** was estimated by comparison of the half-reaction times of each catalyst according to the report of Steglich and Zipse.
18. (a) E. Vedejs, X. Chen, J. Am. Chem. Soc., 118 (1996) 1809–1810; (b) J. C. Ruble, H. A. Latham, G. C. Fu, J. Am. Chem. Soc., 119 (1997) 1492–1493; (c) T. Kawabata, M. Nagato, K. Takasu, K. Fuji, J. Am. Chem. Soc., 119 (1997) 3169–3170; (d) A. C. Spivey, T. Fekner, S. E. Spey, H. Adams, J. Org. Chem., 64 (1999) 9430–9434; (e) G. Naraku, N. Shimomoto, T. Hanamoto, J. Inanaga, Enantiomer, 5 (2000) 135–138; (f) G. Priem, B. Pelotier, S. J. F. Macdonald, M. S. Anson, I. B. Campbell, J. Org. Chem., 68 (2003) 3844–3848; (g) K.-S. Jeong, S.-H. Kim, H.-J. Park, K.-J. Chang, K. S. Kim, Chem. Lett. (2002) 1114–1115; (h) S. Yamada, T. Misono, Y. Iwai, Tetrahedron Lett., 46 (2005) 2239–2242; (i) T. Kawabata, W. Muramatsu, T. Nishio, T. Shibata, H. Schedel, J. Am. Chem. Soc., 129 (2007) 12890–12895; (j) O. C. Dalaigh, S. J. Connon, J. Org. Chem., 72 (2007) 7066–7069; (k) R. P. Wurz, Chem. Rev., 107 (2007) 5570–5595; (l) H. Mandai, K. Fujii, H. Yasuhara, K. Abe, K. Mitsudo, T. Korenaga, S. Suga, *Nature Commun.*, 7 (2016) 11297–11307.

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