

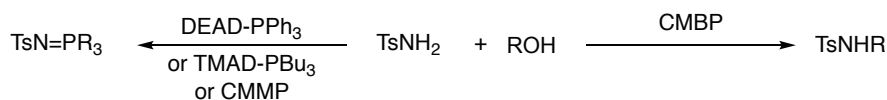
**PIPERIDINE AND AZETIDINE FORMATION BY DIRECT  
CYCLIZATION OF DIOLS WITH *N*-NONSUBSTITUTED  
SULFONAMIDE UNDER THE MITSUNOBU CONDITIONS UTILIZING  
(CYANOMETHYLENE)TRIBUTYLPHOSPHORANE (CMBP) AND ITS  
APPLICATION TO THE SYNTHESIS OF LUPININE**

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**Abstract** – (Cyanomethylene)tributylphosphorane (CMBP) can promote the Mitsunobu reaction of 1,3- and 1,5-diols with *N*-nonsubstituted sulfonamides, such as tosylamide (TsNH<sub>2</sub>) and 3,3-dimethoxypropylsulfonamide (DimpsNH<sub>2</sub>), to prepare azetidine and piperidine ring systems directly. Utilizing this methodology, lupinine, a biologically active piperidine alkaloid, was synthesized.

The synthesis of cyclic amines possessing a wide variety of interesting biological activities has attracted much attention and has been accomplished with the development of efficient synthetic methods.<sup>1</sup> In the course of our studies on the Mitsunobu chemistry, diethyl azodicarboxylate (DEAD)-PPh<sub>3</sub> and our new azodicarboxamide reagents, e.g., *N,N,N',N'*-tetramethylazodicarboxamide<sup>2</sup> (TMAD)-PBU<sub>3</sub> could not promote alkylation of *N*-nonsubstituted sulfonamides such as TsNH<sub>2</sub>, because the amide reacted with PPh<sub>3</sub> or PBU<sub>3</sub> to form triphenyl- or tributylphosphine tosylimide (TsN=PR<sub>3</sub>) under the reaction conditions.<sup>3,4</sup> Furthermore, the same is true with (cyanomethylene)trimethylphosphorane (CMMP), our new phosphorane-type reagent.<sup>5,6</sup> By contrast, the alkylation was accomplished utilizing (cyanomethylene)tributylphosphorane (CMBP)<sup>7</sup> with primary or secondary alcohols to give the desired *N*-monosubstituted sulfonamide in excellent yields.<sup>4</sup> In addition, CMBP could promote the Mitsunobu reaction of 1-phenyl-1,5-pentanediol with TsNH<sub>2</sub> to provide the 2-phenylpiperidine ring system directly (Scheme 1).<sup>4</sup>

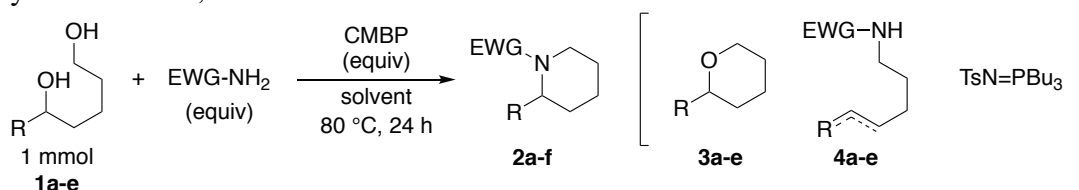


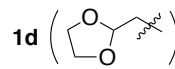
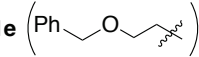
**Scheme 1.** Reaction of *N*-nonsubstituted sulfonamides in Mitsunobu condition

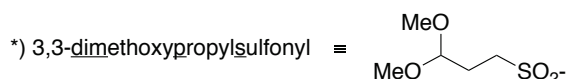
To expand this chemistry, we investigated the reaction of 1,3-, 1,4-, 1,5- and 1,6-diols with TsNH<sub>2</sub> and/or DimpsNH<sub>2</sub>,<sup>8</sup> and applied it to the synthesis of lupinine, a biologically active piperidine alkaloid.<sup>9</sup> The results are described herein.

At first, we focused on the reaction of nonane-1,5-diol (**1a**) with TsNH<sub>2</sub> (1.2–1.5 equiv) using 2.5–3.0 equiv of CMBP at 80 °C under an Ar atmosphere (Table 1, entries 1–3).

**Table 1.** Cyclization of 1,5-diols



entry	diol (R)	EWG- (equiv)	equiv of CMBP	solvent (mL)	product <b>2</b> (% yield)
1	<b>1a</b> ( <i>n</i> Bu)	Ts-(1.5)	3.0	toluene (5)	<b>2a</b> (25)
2	<b>1a</b> ( <i>n</i> Bu)	Ts-(1.2)	2.5	THF (1)	<b>2a</b> (58)
3	<b>1a</b> ( <i>n</i> Bu)	Ts-(1.2)	2.5	1,4-dioxane (1.5)	<b>2a</b> (61)
4	<b>1b</b> (Ph)	Ts-(1.2)	2.5	1,4-dioxane (1.5)	<b>2b</b> (45)
5	<b>1c</b> (PhCH <sub>2</sub> CH <sub>2</sub> -)	Ts-(1.2)	2.5	1,4-dioxane (1.5)	<b>2c</b> (64)
6	<b>1c</b> (PhCH <sub>2</sub> CH <sub>2</sub> -)	Dimps-(1.2)*	2.5	1,4-dioxane (1.5)	<b>2d</b> (50)
7	<b>1d</b> (  )	Dimps-(1.2)	2.5	1,4-dioxane (1.5)	<b>2e</b> (57)
8	<b>1e</b> (  )	Dimps-(1.2)	3.0	1,4-dioxane (1.5)	<b>2f</b> (55)

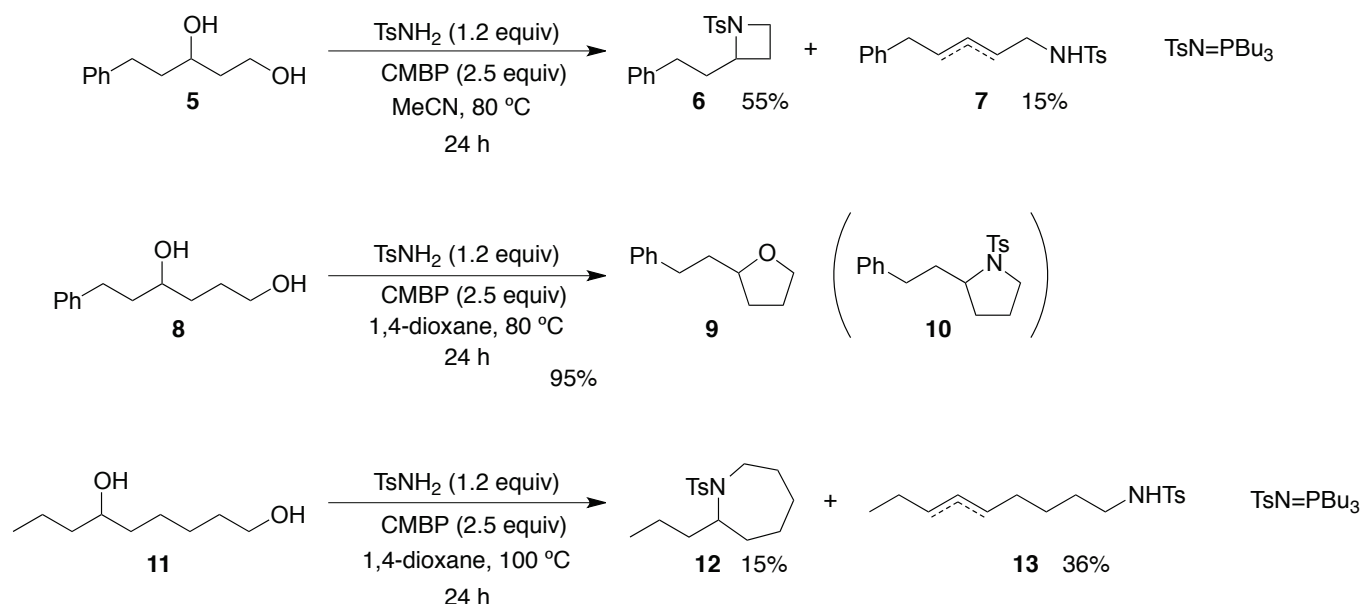


In these reactions, the desired cyclic tosylamide, *N*-tosyl-2-butylpiperidine (**2a**), was produced along with, to some extent, volatile cyclic ether **3a**<sup>10</sup> and olefinic tosylamide **4a**. Furthermore, tributylphosphine tosylimide (TsN=PBu<sub>3</sub>), which was not obtained in the reaction of monoalcohols,<sup>4</sup> was produced to some extent, although the reason was not clear. Finally, the use of dry 1,4-dioxane as a solvent under concentrated conditions (~0.67 mol/L) gave better results to afford a 61% yield of the desired amide **2a** (entry 3). In this reaction, amidation of the primary alcohol moiety was expected in the first step and then secondary hydroxy group was substituted intramolecularly to provide piperidine ring. Unfortunately,

however, intramolecular substitution of activated primary alcohol as a phosphonium by the secondary alcohol took place as competing reaction to give cyclic ether **3a–3e** as a by-product, even in the reaction at ambient temperature.

To confirm the generality of this reaction, we examined the conversion of 1-phenylpentane-1,5-diol (**1b**) to afford *N*-tosyl-2-phenylpiperidine (**2b**) in 45% yield (entry 4) along with a 28% yield of 2-phenyltetrahydropyran (**3b**).<sup>11</sup> In the case of the reaction of a non-benzylic alcohol, 7-phenylheptane-1,5-diol (**1c**), the yield of **2c** exceeded 60% again (entry 5), though the ether **3c**<sup>11</sup> (23%) and olefin **4c** (~5%) were also obtained. The use of DimpsNH<sub>2</sub> and 1,5-diols bearing an acetal **1d** or ethereal moiety **1e** gave virtually the same results (entries 6–8). Although the production of piperidine derivatives utilizing this Mitsunobu methodology halted conclusively in moderate yield, direct cyclization from 1,5-diols was achieved without any time-consuming selective protection-deprotection protocol.

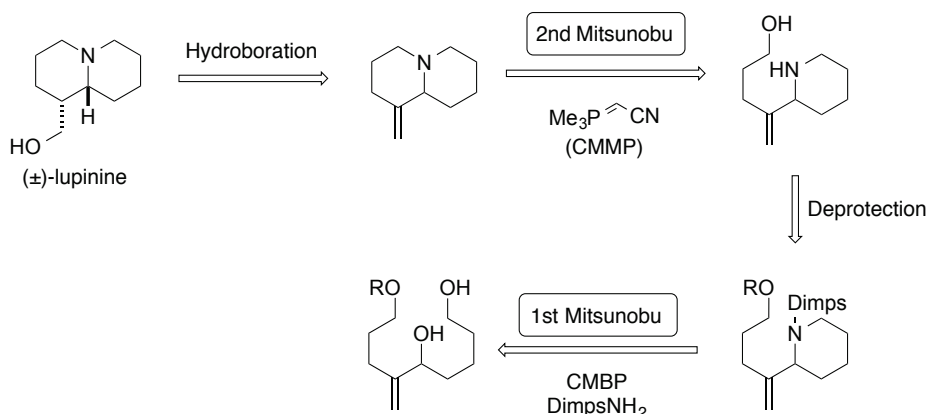
The results of cyclization of 1,3-, 1,4- and 1,6-diols were summarized as follows (Scheme 2): 1) In the case of 5-phenylpentane-1,3-diol (**5**), use of MeCN as a solvent gave better results to form azetidine (**6**) in moderate yield, accompanied by an olefinic amide **7** without any cyclic ether; 2) unfortunately, the reaction of 6-phenylhexane-1,4-diol (**8**) gave a cyclic ether,<sup>12</sup> 2-(2-phenylethyl)tetrahydrofuran (**9**),<sup>13</sup> as a major product without any desired pyrrolidine derivative (**10**); and 3) the formation of azepane **12** from 1,6-diol **11** gave the unsatisfactory outcome of providing only a 15% yield along with a 36% yield of eliminated compound **13**.



**Scheme 2.** Cyclization of 1,3-, 1,4- and 1,6-diols

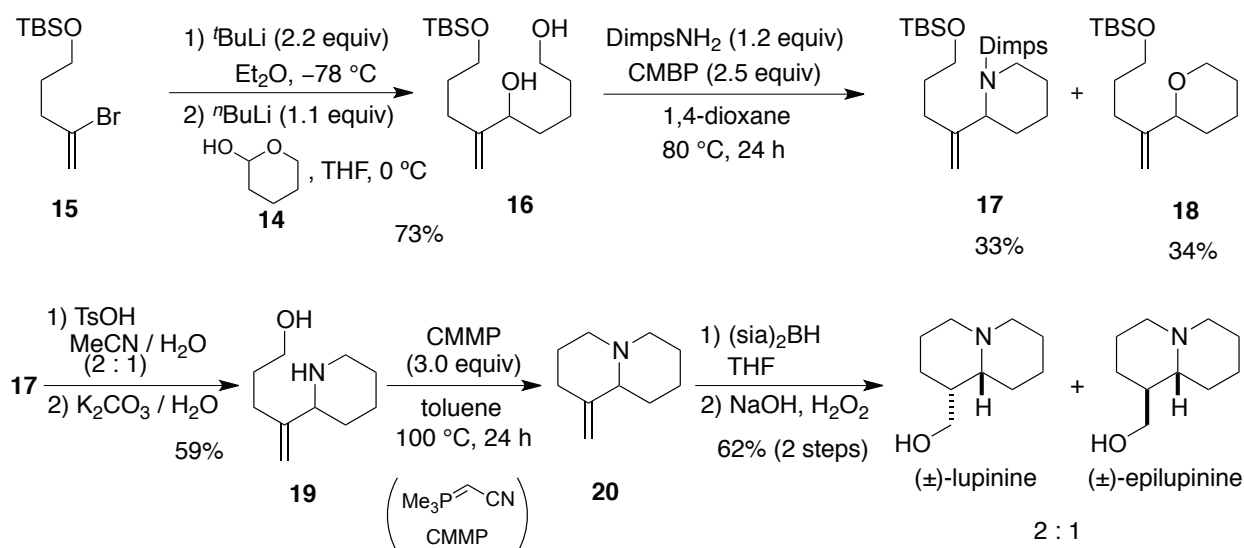
As a synthetic application of the present reaction, lupinine, a quinolizidine alkaloid from genus *Lupinus*, was synthesized utilizing Dimps methodology in short steps. Our retrosynthetic analysis of lupinine is illustrated in Scheme 3. The quinolizine skeleton could be constructed by direct cyclization of 1,5-diol

with Dimps amide (1st Mitsunobu) and intramolecular cyclization of 1,5-aminoalcohol (2nd Mitsunobu) utilizing a couple of Mitsunobu reaction employing phosphorane-type reagents.



**Scheme 3.** Retrosynthesis of lupinine

The synthesis started from 2-lithiooxytetrahydropyran<sup>14</sup> prepared by the lithiation of 2-hydroxytetrahydropyran (**14**), which was easily converted to 1,5-diol **16** by the addition of alkenyl-lithium derived from alkenyl bromide **15**<sup>15</sup> with *t*-butyllithium. The diol **16** was treated with DimpsNH<sub>2</sub> in the presence of CMBP (2.5 equiv) at 80 °C to afford the desired piperidine derivative **17** along with cyclic ether **18**. Both Dimps and TBDMS groups of **17** were removed successfully and simultaneously by the treatment in aqueous MeCN solution under acidic (*p*-TsOH) followed by basic (K<sub>2</sub>CO<sub>3</sub>) conditions in one pot to give alcohol **19**.<sup>8</sup> The cyclization of **19** was accomplished by intramolecular Mitsunobu reaction using (cyanomethylene)trimethylphosphorane (CMMP) at 100 °C under an Ar atmosphere.<sup>16</sup> Finally, hydroboration/oxidation of the *exo*-methylene moiety of **20** gave a 2 : 1 mixture of lupinine and epilupinine (Scheme 4).<sup>17</sup>



**Scheme 4.** Synthesis of lupinine

In summary, we have developed the direct cyclization of 1,3- and 1,5-diols to prepare azetidine and piperidine derivatives and achieved a concise synthesis of lupinines utilizing Dimps strategy combined with the Mitsunobu protocol. Further work on the synthesis of other nitrogen-containing compounds utilizing this chemistry is in progress.

## EXPERIMENTAL

**General.** Melting points were determined on a Yanaco MP-3 or Büchi B-545 apparatus, and were uncorrected. Infrared (IR) spectra were recorded using the with a JASCO Model FTIR-4200 spectrophotometer. Proton nuclear magnetic resonance spectra ( $^1\text{H}$  NMR) were recorded with Varian Mercury-300 (300 MHz), Varian 400 MR (400 MHz) or Varian Unity-600 (600 MHz) spectrometers in  $\text{CDCl}_3$ . Chemical shifts are reported in parts per million on the  $\delta$  scale relative to the internal standard  $\text{Me}_4\text{Si}$  ( $\delta = 0.00$  ppm), and coupling constants are given in Hertz.  $^{13}\text{C}$  NMR spectra were obtained with Varian Mercury-300 (75 MHz), Varian 400 MR (100 MHz) or Varian Unity 600 (150 MHz) instrument, and chemical shifts are referenced to the residual solvent signal ( $\text{CDCl}_3$ ;  $\delta = 77.0$  ppm). Mass spectra, including high-resolution mass spectra, were recorded with a JEOL AX-500 or JMS-700 spectrometer. Unless otherwise noted, all reactants or reagents including solvents were obtained from commercial suppliers and used as received. Diol **1d** and **1e** were prepared by Baeyer-Villiger oxidation of 2-(1,3-dioxan-2-ylmethyl)cyclopentanone<sup>18</sup> and 2-(2-benzyloxyethyl)cyclopentanone,<sup>19</sup> respectively. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F-254 plates (0.2 mm layers) on glass with a fluorescent indicator, supplied by E. Merck. For column chromatography, Fuji Silysia BW-127ZH (100– 270 mesh) silica was used.

**General procedure for Mitsunobu cyclization of diols.** An Ace pressure tube was used as a reaction vessel. To a solution of diol (1.0 mmol) and *N*-nonsubstituted sulfonamide (e.g.  $\text{TsNH}_2$ ) (1.2 mmol) in dry 1,4-dioxane (1.5 mL) was added CMBP (666  $\mu\text{L}$ , 2.5 mmol) at ambient temperature under an argon atmosphere. The resulting mixture was sealed and stirred for 24 h at 80~100 °C. After concentrating *in vacuo*, the residue was purified by silica gel column chromatography (eluent: hexane only- hexane/AcOEt, 20/1 - 10/1, v/v) to yield a *N*-sulfonated cyclic amine.

***N*-Tosyl-2-butylpiperidine (2a).** The title compound was isolated as a colorless oil.;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.71 (d, 2H,  $J = 8.4$  Hz), 7.27 (d, 2H,  $J = 8.4$  Hz), 3.99–4.02 (m, 1H), 3.75 (dd, 1H,  $J = 13.8$ , 3.6 Hz), 2.98 (ddd, 1H,  $J = 13.8$ , 13.8, 3.0 Hz), 2.42 (s, 3H), 1.54–1.61 (m, 1H), 1.39–1.52 (m, 6H), 1.19–1.32 (m, 5H), 0.86 (t, 3H,  $J = 6.6$  Hz);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  142.7, 139.1, 129.5, 127.0, 53.0, 40.6, 29.1, 28.6, 27.4, 24.5, 22.5, 21.5, 18.4, 14.0; IR (neat) 3025, 2933, 2860, 1598, 1455, 1383, 1335, 1304, 1208, 1190, 1149, 1093, 1045, 1018, 944, 927, 876, 813, 791, 752, 712, 693, 654, 600, 551;

MS (EI)  $m/z$  295  $[M]^+$ , 238 (base peak), 155, 139, 91, 84, 65, 55; HRMS (EI)  $m/z$  calcd for  $C_{16}H_{25}NO_2S$   $[M]^+$ : 295.1606; found 295.1611.

***N*-Tosyl-2-phenylpiperidine (2b)**. The title compound was isolated as colorless needles.; mp 137–138 °C;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  7.74–7.77 (m, 2H), 7.22–7.35 (m, 7H), 5.27 (brd, 1H,  $J = 4.8$  Hz), 3.84 (ddd, 1H,  $J = 14.4, 3.6, 1.2$  Hz), 3.01 (ddd, 1H,  $J = 14.4, 13.2, 3.0$  Hz), 2.44 (s, 3H), 2.18–2.23 (m, 1H), 1.63–1.70 (m, 1H), 1.47–1.53 (m, 1H), 1.36–1.44 (m, 2H), 1.25–1.34 (m, 1H);  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  142.9, 138.9, 138.8, 129.7, 128.6, 127.0, 127.0, 126.8, 55.3, 41.9, 27.3, 24.3, 21.5, 19.0; IR (neat) 2929, 2868, 1598, 1495, 1448, 1335, 1303, 1220, 1187, 1170, 1151, 1102, 1092, 1050, 1027, 945, 850, 816, 792, 756, 721, 697, 664, 633, 554, 539  $cm^{-1}$ ; MS (EI)  $m/z$  315 ( $[M]^+$ ), 238, 160, 91 (base peak); HRMS (EI)  $m/z$  calcd for  $C_{18}H_{21}NO_2S$   $[M]^+$ : 315.1293; found 315.1291.

***N*-Tosyl-2-(2-phenylethyl)piperidine (2c)**. The title compound was isolated as colorless needles.; mp 114–115 °C;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  7.72 (d, 2H,  $J = 7.8$  Hz), 7.25–7.29 (m, 4H), 7.13–7.20 (m, 3H), 4.06–4.12 (m, 1H), 3.81 (br dd 1H,  $J = 13.2, 3.6$  Hz), 3.02 (ddd, 1H,  $J = 14.4, 13.2, 2.4$  Hz), 2.55–2.66 (m, 2H), 2.42 (s, 3H), 1.89–1.96 (m, 1H), 1.69–1.76 (m, 1H), 1.41–1.55 (m, 5H), 1.19–1.27 (m, 1H);  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  142.8, 141.9, 139.0, 129.7, 128.39, 128.37, 127.0, 125.9, 52.8, 40.7, 32.9, 31.7, 27.6, 24.4, 21.5, 18.5; IR (neat) 2939, 2862, 1496, 1454, 1383, 1336, 1303, 1213, 1151, 1125, 1093, 1054, 1025, 990, 970, 926, 881, 815, 749, 727, 712, 694, 652, 603, 584, 551, 538, 505  $cm^{-1}$ ; MS (EI)  $m/z$  343 ( $[M]^+$ ), 238 (base peak), 155, 91; HRMS (EI)  $m/z$  calcd for  $C_{20}H_{25}NO_2S$   $[M]^+$ : 343.1606; found 343.1614.

***N*-(3,3-Dimethoxypropylsulfonyl)-2-(2-phenylethyl)piperidine (2d)**. The title compound was isolated as a colorless oil.;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  7.27–7.30 (m, 2H), 7.17–7.22 (m, 3H), 4.47 (t, 1H,  $J = 5.4$  Hz), 3.98–4.02 (m, 1H), 3.67 (dd, 1H,  $J = 14.4, 3.6$  Hz), 3.35 (s, 6H), 3.07 (ddd, 1H,  $J = 13.2, 2.4, 2.4$  Hz), 2.99 (t, 2H,  $J = 7.8$  Hz), 2.60–2.69 (m, 2H), 2.02–2.15 (m, 3H), 1.84–1.90 (m, 1H), 1.48–1.75 (m, 6H);  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  141.7, 128.4, 128.3, 126.0, 102.9, 53.8, 53.7, 52.8, 48.5, 40.7, 33.0, 32.0, 28.5, 27.3, 25.6, 18.5; IR (neat) 2936, 2866, 1497, 1455, 1385, 1317, 1280, 1190, 1168, 1140, 1121, 1071, 1057, 1026, 971, 928, 883, 817, 799, 789, 751, 700, 617, 604, 593, 585, 563, 554; MS (EI)  $m/z$  355  $[M]^+$ , 323, 260, 250, 236, 218, 188, 167, 154, 105, 91, 84 (base peak), 71, 41; HRMS (EI)  $m/z$  calcd for  $C_{18}H_{29}NO_4S$   $[M]^+$ : 355.1817; found 355.1808.

***N*-(3,3-Dimethoxypropylsulfonyl)-2-(1,3-dioxan-2-ylmethyl)piperidine (2e)**. The title compound was isolated as a colorless oil.;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  4.90 (t, 1H,  $J = 4.4$  Hz), 4.44 (t, 1H,  $J = 5.3$  Hz), 4.16–4.19 (m, 1H), 3.93–3.98 (m, 2H), 3.80–3.87 (m, 2H), 3.67 (dd, 1H,  $J = 14.5, 3.1$  Hz), 3.33 (s, 6H), 2.99–3.03 (m, 3H), 1.98–2.13 (m, 3H), 1.87 (ddd, 1H,  $J = 14.0, 6.6, 6.6$  Hz), 1.72–1.77 (m, 1H), 1.49–1.69 (m, 5H);  $^{13}C$  NMR (150 MHz,  $CDCl_3$ )  $\delta$  102.9, 102.5, 64.8, 53.7, 53.6, 49.3, 48.3, 40.9, 34.5, 29.3, 27.2, 25.8, 18.6; IR (neat) 2940, 2888, 1447, 1413, 1386, 1317, 1280, 1236, 1190, 1139, 1119, 1056,

1030, 971, 921, 879, 791, 749, 666, 528  $\text{cm}^{-1}$ ; MS (CI)  $m/z$  336  $[\text{M}-\text{H}]^+$ , 306, 250, 242, 218, 210, 170, 154, 84 (base peak), 71; HRMS (CI)  $m/z$  calcd for  $\text{C}_{14}\text{H}_{26}\text{NO}_6\text{S}$   $[\text{M}-\text{H}]^+$ : 336.1481; found 336.1485.

***N*-(3,3-Dimethoxypropylsulfonyl)-2-(2-benzyloxyethyl)piperidine (2f)**. The title compound was isolated as a colorless oil.;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32–7.34 (m, 4H), 7.26–7.29 (m, 1H), 4.53 (d, 1H,  $J = 12.0$  Hz), 4.47 (d, 1H,  $J = 12.0$  Hz), 4.44 (t, 1H,  $J = 10.8$  Hz), 4.10–4.15 (m, 1H), 3.67 (dd, 1H,  $J = 14.4, 3.6$  Hz), 3.54 (t, 2H,  $J = 6.6$  Hz), 3.34 (s, 6H), 2.99–3.02 (m, 3H), 2.02–2.11 (m, 3H), 1.84 (dddd, 1H,  $J = 13.2, 6.6, 6.6, 6.6$  Hz), 1.70–1.76 (m, 1H), 1.46–1.68 (m, 5H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  138.4, 128.4, 127.7, 127.6, 102.9, 73.1, 67.4, 53.8, 53.7, 50.2, 48.4, 40.7, 30.2, 28.8, 27.3, 25.7, 18.6; IR (neat) 3017, 2940, 2862, 1454, 1361, 1319, 1281, 1236, 1213, 1190, 1121, 1073, 952, 923, 880, 793, 740, 698, 666, 531  $\text{cm}^{-1}$ ; MS (CI)  $m/z$  384  $[\text{M}-\text{H}]^+$ , 354, 290, 258, 250, 218 (base peak), 198, 176, 154, 91, 84, 71; HRMS (MALDI)  $m/z$  calcd for  $\text{C}_{19}\text{H}_{31}\text{NO}_5\text{SNa}$   $[\text{M}+\text{Na}]^+$ : 408.1821; found 408.1815.

***N*-Tosyl-2-(2-phenylethyl)azetidide (6)**. The title compound was isolated as colorless needles.; mp 98–99  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.58–7.62 (m, 2H), 7.13–7.31 (m, 7H), 3.81–3.87 (m, 1H), 3.64–3.69 (m, 1H), 3.45–3.50 (m, 1H), 2.64–2.70 (m, 1H), 2.55–2.61 (m, 1H), 2.43 (s, 3H), 2.18–2.24 (m, 1H), 1.96–2.03 (m, 1H), 1.85–1.91 (m, 2H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  143.8, 141.2, 132.0, 129.6, 128.44, 128.41, 128.39, 126.0, 63.4, 47.6, 37.4, 30.6, 22.2, 21.6; IR (neat) 2925, 1598, 1495, 1453, 1341, 1160, 1092, 1030, 943, 817, 700, 666, 607, 553, 521  $\text{cm}^{-1}$ ; MS (EI)  $m/z$  315 ( $[\text{M}]^+$ ), 210, 184, 160 (base peak), 155, 91; HRMS (EI)  $m/z$  calcd for  $\text{C}_{18}\text{H}_{21}\text{NO}_2\text{S}$   $[\text{M}]^+$ : 315.1293; found 315.1287.

***N*-Tosyl-2-propylazepane (12)**. The title compound was isolated as a colorless oil.:  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (d, 2H,  $J = 8.4$  Hz), 7.27 (d, 2H,  $J = 8.4$  Hz), 3.84–3.90 (m, 1H), 3.76 (ddd, 1H,  $J = 15.6, 3.6, 3.6$  Hz), 2.90 (ddd, 1H,  $J = 15.6, 12.0, 2.4$  Hz), 2.41 (s, 3H), 2.02–2.08 (m, 1H), 1.54–1.72 (m, 4H), 1.30–1.40 (m, 3H), 1.16–1.25 (m, 4H), 0.81 (t, 3H,  $J = 7.2$  Hz);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  142.6, 139.3, 129.4, 127.2, 56.7, 43.2, 36.9, 34.5, 29.4, 29.1, 24.1, 21.5, 19.2, 14.0; IR (neat) 2927, 2857, 1598, 1494, 1453, 1330, 1241, 1211, 1150, 1091, 1060, 1024, 1016, 930, 886, 863, 814, 752, 711, 689, 652, 573, 551; MS (EI)  $m/z$  295  $[\text{M}]^+$ , 252 (base peak), 238, 155, 140, 96, 91, 55, 41; HRMS (EI)  $m/z$  calcd for  $\text{C}_{16}\text{H}_{25}\text{NO}_2\text{S}$   $[\text{M}]^+$ : 295.1606; found 295.1597.

**9-(*tert*-Butyldimethylsilyloxy)-6-methylenonane-1,5-diol (16)**. To a solution of **15**<sup>13</sup> (529 mg, 1.89 mmol) in dry  $\text{Et}_2\text{O}$  (25 mL) was added *t*-BuLi (1.62 M in heptane, 2.46 mL, 3.99 mmol) at  $-78$   $^\circ\text{C}$  under an argon atmosphere. The mixture was stirred for 1 h and then poured via cannula into a solution of **14** (191 mg, 1.87 mmol) in dry THF (10 mL) which was treated with *n*-BuLi (1.60 M in hex., 1.28 mL, 2.05 mmol) at  $0$   $^\circ\text{C}$  for 30 min. After stirring, the resulting mixture was quenched with 15 mL of a saturated  $\text{NH}_4\text{Cl}$  aqueous solution and extracted with AcOEt (40 mL  $\times$  3), and the organic extracts were dried over  $\text{MgSO}_4$ , filtered and concentrated. The residue was purified by silica gel column chromatography ( $\text{CHCl}_3$ /



Et<sub>2</sub>O = 5/1, then 4/1, v/v) to give diol **16** in 73% yield (417 mg) as a colorless oil.; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 5.00 (brs, 1H), 4.82 (brs, 1H), 4.03–4.06 (m, 1H), 3.58–3.63 (m, 5H), 2.09–2.14 (m, 1H), 1.99–2.04 (m, 1H), 1.32–1.74 (m, 9H), 0.87 (s, 9H), 0.30 (s, 6H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 151.5, 109.6, 75.3, 62.9, 62.4, 35.0, 32.4, 31.2, 27.6, 25.9, 21.8, 18.3, –5.3; IR (neat) 3341, 2929, 2858, 1647, 1462, 1254, 1214, 1098, 901, 835, 755, 666 cm<sup>-1</sup>; MS (CI) *m/z* 303 [M+H]<sup>+</sup>, 285, 245, 227, 153 (base peak), 135, 71; HRMS (CI) *m/z* calcd for C<sub>16</sub>H<sub>35</sub>O<sub>3</sub>Si [M+H]<sup>+</sup>: 303.2350; found 303.2364.

**Mitsunobu cyclization of diol 16: 2-[5-(*tert*-Butyldimethylsilyloxy)pent-1-en-2-yl]-*N*-(3,3-dimethoxypropylsulfonyl)piperidine (**17**).** The cyclization was carried out using 120 mg of **16** (0.40 mmol) and 89.9 mg of DimpsNH<sub>2</sub> (0.49 mmol) according to the general procedure. After purification by silica gel column chromatography (eluent: *n*-hexane/AcOEt = 20/1, 10/1 then 5/1, v/v), 39 mg of **18** (34%) and 59 mg of desired **17** (33%) were obtained as a pale yellow oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 5.10 (brs, 1H), 5.07 (brd, 1H, *J* = 1.3 Hz), 4.47–4.48 (m, 2H), 3.60–3.67 (m, 3H), 3.36 (s, 6H), 3.10 (ddd, 1H, *J* = 15.3, 12.3, 3.1 Hz), 3.03 (t, 2H, *J* = 7.9 Hz), 2.01–2.16 (m, 5H), 1.46–1.74 (m, 7H), 0.89 (s, 9H), 0.05 (s, 6H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 145.4, 112.3, 102.9, 62.6, 56.2, 53.8, 48.6, 41.9, 31.0, 30.1, 27.3, 27.1, 26.0, 25.7, 19.3, 18.3, –5.3; IR (neat) 2931, 2857, 1645, 1462, 1444, 1335, 1323, 1252, 1191, 1099, 1057, 963, 835, 788, 719, 668, 524 cm<sup>-1</sup>; MS (CI) *m/z* 449 [M]<sup>+</sup>, 448 [M–H]<sup>+</sup>, 434, 392 (base peak), 386, 360, 254, 135, 71; HRMS (CI) *m/z* calcd for C<sub>21</sub>H<sub>43</sub>NO<sub>5</sub>SSi [M]<sup>+</sup>: 449.2631; found 449.2629. **18** colorless oil; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 5.00 (brs, 1H), 4.80 (brd, 1H, *J* = 1.2 Hz), 4.02 (ddd, 1H, *J* = 11.4, 4.2, 1.8 Hz), 3.67 (brd, 1H, *J* = 10.2 Hz), 3.61 (brt, 2H, *J* = 6.6 Hz), 3.46 (ddd, 1H, *J* = 11.4, 11.4, 1.8 Hz), 2.03–2.13 (m, 2H), 1.84–1.87 (m, 1H), 1.64–1.70 (m, 3H), 1.47–1.59 (m, 3H), 1.35–1.42 (m, 1H), 0.86 (s, 9H), 0.03 (s, 6H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 150.3, 109.1, 80.4, 68.8, 62.9, 31.3, 31.1, 28.8, 26.1, 26.0, 23.9, 18.4, –5.2; IR (neat) 2931, 2855, 1649, 1471, 1462, 1439, 1387, 1255, 1204, 1090, 1053, 1039, 975, 898, 835, 776 cm<sup>-1</sup>; MS (CI) *m/z* 285 [M+H]<sup>+</sup>, 269, 227 (base peak), 197, 185, 153, 135, 107, 93, 75, 41; HRMS (CI) *m/z* calcd for C<sub>16</sub>H<sub>33</sub>O<sub>2</sub>Si [M+H]<sup>+</sup>: 285.2252; found 285.2248.

**4-(Piperidin-2-yl)pent-4-en-1-ol (**19**).** To a solution of **17** (159 mg, 0.35 mmol) in MeCN (2.4 mL) and water (1.2 mL) was added slowly *p*-toluenesulfonic acid monohydrate (204 mg, 1.07 mmol) at 0 °C. After 5 min, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. After completion of the reaction was checked by TLC, the mixture was cooled again at 0 °C, and then water (1 mL) and K<sub>2</sub>CO<sub>3</sub> (259 mg, 1.87 mmol) were added slowly to the mixture. After stirring for 10 min at 0 °C and 1 h at ambient temperature, NaOH (5 g) and an aqueous NaOH solution (6 M, 10 mL) was added and the mixture was extracted with CHCl<sub>3</sub> (3 x 10 mL). The combined organic extracts were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was subjected to purification by column chromatography on silica gel (treated with NH<sub>3</sub>, eluent: AcOEt/MeOH = 2/1, v/v) to afford 35 mg (59 %) of **19** as a colorless oil.; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 5.02 (brs, 1H), 4.80 (brd, 1H, *J* = 1.3 Hz),



3.65 (t, 2H,  $J = 6.0$  Hz), 3.14 (dddd, 1H,  $J = 11.8, 3.7, 1.9, 1.9$  Hz), 3.02 (dd, 1H,  $J = 11.2, 2.5$  Hz), 2.67 (ddd, 1H,  $J = 11.9, 11.9, 4.8$  Hz), 2.23 (dddd, 1H,  $J = 15.1, 8.0, 8.0, 0.8$  Hz), 2.14 (dddd, 1H,  $J = 15.0, 6.1, 6.1, 0.8$  Hz), 2.07 (brs, 2H), 1.83–1.87 (m, 1H), 1.68–1.80 (m, 3H), 1.60–1.63 (m, 1H), 1.38–1.44 (m, 2H), 1.32–1.37 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  151.8, 109.8, 62.3, 61.8, 47.3, 31.7, 31.4, 29.1, 26.1, 25.0; IR (neat) 3283, 2930, 2853, 1644, 1440, 1059, 892, 790, 758  $\text{cm}^{-1}$ ; MS (EI)  $m/z$  169  $[\text{M}]^+$ , 124, 84 (base peak), 80; HRMS (EI)  $m/z$  calcd for  $\text{C}_{10}\text{H}_{19}\text{NO}$   $[\text{M}]^+$ : 169.1467; found 169. 1475.

### Synthesis of lupinine and epilupinine from **19**.

**1-Methyleneoctahydro-2H-quinolizine (20)**. An Ace pressure tube was used as a reaction vessel. To a solution of **19** (65 mg, 0.38 mmol) in dry toluene (5 mL) was quickly added solid CMMP<sup>6b</sup> (134 mg, 1.16 mmol) in a vial at ambient temperature under an argon atmosphere. The resulting mixture was sealed and stirred for 24 h at 100 °C. The residue was directly subjected to purification by column chromatography on silica gel (treated with  $\text{NH}_3$ , eluent: petroleum ether then  $\text{Et}_2\text{O}$ ) to afford **20** containing a solvent. It was applied to following next reaction without further concentration. **20** pale yellow oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  4.76 (dd, 2H,  $J = 6.6, 1.8$  Hz), 2.87–2.89 (m, 2H), 2.35–2.39 (m, 1H), 2.22 (brd, 1H,  $J = 11.4$  Hz), 2.18 (ddd, 1H,  $J = 11.4, 11.4, 3.6$  Hz), 2.01–2.11 (m, 2H), 1.81–1.85 (m, 2H), 1.67–1.72 (m, 2H), 1.59–1.63 (m, 2H), 1.49–1.56 (m, 1H), 1.27–1.35 (m, 1H);  $^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ )  $\delta$  148.3, 106.9, 64.6, 57.3, 56.8, 35.1, 28.5, 26.9, 25.6, 24.5; IR (neat) 2936, 2857, 2801, 2754, 1649, 1443, 1348, 1325, 1282, 1178, 1122, 1109, 1077, 1054, 1016, 975, 899, 875, 732, 641, 552  $\text{cm}^{-1}$ ; MS (EI)  $m/z$  151 ( $[\text{M}]^+$ , base peak), 136, 122, 109, 95, 43; HRMS (EI)  $m/z$  calcd for  $\text{C}_{10}\text{H}_{17}\text{N}$   $[\text{M}]^+$ : 151.1361; found 151.1369.

**Hydroboration/oxidation of 20**. To a solution of **20** in dry THF (1.6 mL) was added disiamylborane (2.0 M in  $\text{CH}_2\text{Cl}_2$ , 760  $\mu\text{L}$ , 1.52 mmol) at 0 °C under an argon atmosphere. The mixture was stirred for 1 h at ambient temperature and cooled again at 0 °C. To the resulting mixture were added 2.5 mL of an aqueous NaOH solution (3 M) and then 560  $\mu\text{L}$  of a 30%  $\text{H}_2\text{O}_2$  solution. After stirring for 19 h at ambient temperature, the mixture was treated with 40 mg of  $\text{Na}_2\text{SO}_3$  for 10 min and then diluted with  $\text{Et}_2\text{O}$  (10 mL). The resulting mixture was extracted with an aqueous HCl solution (6 M, 3 x 10 mL). The combined aqueous layers were basified with an aqueous NaOH solution (6 M) and extracted with  $\text{Et}_2\text{O}$  (3 x 100 mL). The ethereal solution was dried over  $\text{MgSO}_4$ , filtered, and concentrated under reduced pressure. The residue was subjected to purification by column chromatography on silica gel (treated with  $\text{NH}_3$ , eluent: AcOEt/MeOH = 5/1 the 4/1, v/v) to afford a 2 : 1 mixture (by  $^1\text{H}$  NMR) of lupinine and epilupinine (32 mg, 62% in 2 steps from **19**). All spectroscopic data ( $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR, and MS/HRMS) for synthetic lupinine and epilupinine agreed with those reported previously in the literature.<sup>17</sup> lupinine : epilupinine = 74 : 26. Pale yellow oil;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  4.15 (dd, 0.74H,  $J = 10.7, 3.0$  Hz), 3.70 (d, 0.74H,  $J = 10.7$  Hz), 3.67 (dd, 0.26H,  $J = 11.0, 3.7$  Hz), 3.62 (dd, 0.26H,  $J = 11.0, 5.3$  Hz), 2.92–3.00 (m, 0.52H),

2.82–2.89 (m, 1.48H), 2.65, (brs, 0.26H), 2.10–2.21 (m, 1.48H), 2.01–2.09 (m, 0.52H), 1.52–1.96 (m, 10.96H), 1.23–1.34 (m, 1.78H); <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 65.9, 65.0, 64.4, \* 64.1, \* 57.0 (×2), 56.5, \* 56.0, \* 43.2, \* 38.2, 31.3, 29.6, 29.0, \* 27.7, \* 25.5, 24.6, \* 24.5, 24.24, \* 24.23, \* 22.9; IR (neat) 3348, 2930, 2856, 2806, 2760, 1576, 1443, 1396, 1351, 1294, 1181, 1113, 1088, 1066, 1036, 939, 922, 877, 757, 727, 694, 580, 561, 549 cm<sup>-1</sup>; MS (EI) *m/z* 169 [M]<sup>+</sup>, 168, 152 (base peak), 138, 124, 110, 97, 83, 55; HRMS (EI) *m/z* calcd for C<sub>10</sub>H<sub>19</sub>NO [M]<sup>+</sup>: 169.1467; found 169.1469. (\* = epilupinine)

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## REFERENCES AND NOTES

- (a) N. J. Turner and M. D. Truppo ‘Chiral Amine Synthesis: Methods, Developments and Applications’. Wiley-VCH; Weinheim, Germany: 2010, and references cited therein; (b) A. Hameed, S. Javed, R. Noreen, T. Huma, S. Iqbal, H. Umbreen, T. Gulzar, and T. Farooq, *Molecules*, 2017, **22**, 1; (c) The excellent direct cyclization of diols to prepare cyclic amine derivatives using metal catalysts were reported, see A. Enomoto, T. Shimbayashi, and K. Fujita, *Heterocycles*, 2019, **98**, 1119, and references cited therein.
- (a) T. Tsunoda, J. Otsuka, Y. Yamamiya, and S. Itô, *Chem. Lett.*, 1994, **23**, 539; (b) T. Tsunoda and H. Kaku, “*N,N,N,N*-Tetramethylazodicarboxamide,” *Electronic Encyclopedia of Reagents for Organic Synthesis (e-EROS)*, ed. by L. Paquette, John Wiley & Sons, Ltd., West Sussex, UK, 2003.
- S. Bittner, Y. Assaf, P. Krief, M. Pomerantz, B. T. Ziemnicka, and C. G. Smith, *J. Org. Chem.*, 1985, **50**, 1712.
- T. Tsunoda, H. Yamamoto, K. Goda, and S. Itô, *Tetrahedron Lett.*, 1996, **37**, 2457.
- Unpublished results carried out by our group.
- (a) T. Tsunoda, C. Nagino, M. Oguri, and S. Itô, *Tetrahedron Lett.*, 1996, **37**, 2459; (b) I. Sakamoto, H. Kaku, and T. Tsunoda, *Chem. Pharm. Bull.*, 2003, **51**, 474.
- I. Sakamoto, T. Nishii, F. Ozaki, H. Kaku, M. Tanaka, and T. Tsunoda, *Chem. Pharm. Bull.*, 2005, **53**, 1508.
- 3,3-Dimethoxypropylsulfonyl (Dimps) group (**3**), which could be removed easily under acidic followed by basic conditions in an aqueous solution, was developed as a new versatile sulfonyl group for amino activation/protection. See, I. Sakamoto, K. Iwaoka, Y. Kawada, T. Naito, K. Makida, Y. Takeuchi, T. Nishii, M. Horikawa, H. Kaku, and T. Tsunoda, *Tetrahedron*, 2018, **74**, 3052.

9. (a) J. P. Michael, *Nat. Prod. Rep.*, 2003, **20**, 458; (b) J. P. Michael, *Nat. Prod. Rep.*, 2008, **25**, 139; (c) O. B. Abdel-Halim, A. A. El-Gammal, H. Abdel-Fattah, and K. Takeya, *Phytochemistry*, 1999, **51**, 5; (d) Synthesis of lupinine; S. G. Davies, A. M. Fletcher, E. M. Foster, I. T. T. Houlsby, P. M. Roberts, T. M. Schofield, and J. E. Thomson, *Chem. Commun.*, 2014, **50**, 8309, and references cited therein; (e) Synthesis of epilupinine: T. Tsutsumi, S. Karanjit, A. Nakayama, and K. Namba, *Org. Lett.*, 2019, **21**, 2620, and references cited therein.
10. We previously reported that CMBP or CMMP promoted the cyclization of 1,5-diols to give cyclic ethers in good yields. See T. Tsunoda, F. Ozaki, N. Shirakata, Y. Tamaoka, H. Yamamoto, and S. Itô, *Tetrahedron Lett.*, 1996, **37**, 2463.
11. H. Ishikawa, T. Mukaiyama, and S. Ikeda, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 776.
12. The formation of tetrahydrofuran ring is much faster than the intermolecular substitution of sulfonamide. Furthermore, it is well known that the rate of cyclization to five-membered ring is faster than that to six-membered ring in the reaction of  $\omega$ -chloroalcohols. See W. H. Richardson, C. M. Golino, R. H. Wachs, and M. B. Yelvington, *J. Org. Chem.*, 1971, **36**, 943.
13. M. Aquino, S. Cardani, G. Fronza, C. Fuganti, R. P. Fernandez, and A. Tagliani, *Tetrahedron*, 1991, **47**, 7887.
14. In order to save the alkenyllithium derived from alkenyl bromide **15**, lithiated 2-hydroxytetrahydropyran which was an equivalent of an open chain aldehyde was prepared at first, see a similar method, T. Kawashima, M. Nakamura, and N. Inamoto, *Heterocycles*, 1997, **44**, 487.
15. R. A. Swyka, W. G. Shuler, B. J. Spinello, W. Zhang, C. Lan, and M. J. Krische, *J. Am. Chem. Soc.*, 2019, **141**, 6864.
16. CMMP mediated the cyclization of amino alcohols to give cyclic amines in good yields, see ref. 10.
17. The structures of lupinine and epilupinine were confirmed by comparison with  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of each authentic sample, see A. C. Cutter, I. R. Miller, J. F. Keily, R. K. Bellingham, M. E. Light, and R. C. D. Brown, *Org. Lett.*, 2011, **13**, 3988.
18. G. Conole, R. J. Mears, H. De Silva, and A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1995, 1825.
19. S. Pichette, D. K. Winter, J. Lessard, and C. Spino, *J. Org. Chem.*, 2013, **78**, 12532.