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FACILE AND SHORT-STEP SYNTHESIS OF 5-SUBSTITUTED 2,3,4,5-TETRAHYDROBENZO[*f*][1,4]OXAZEPINES USING A MODIFIED PICTET-SPENGLER REACTION

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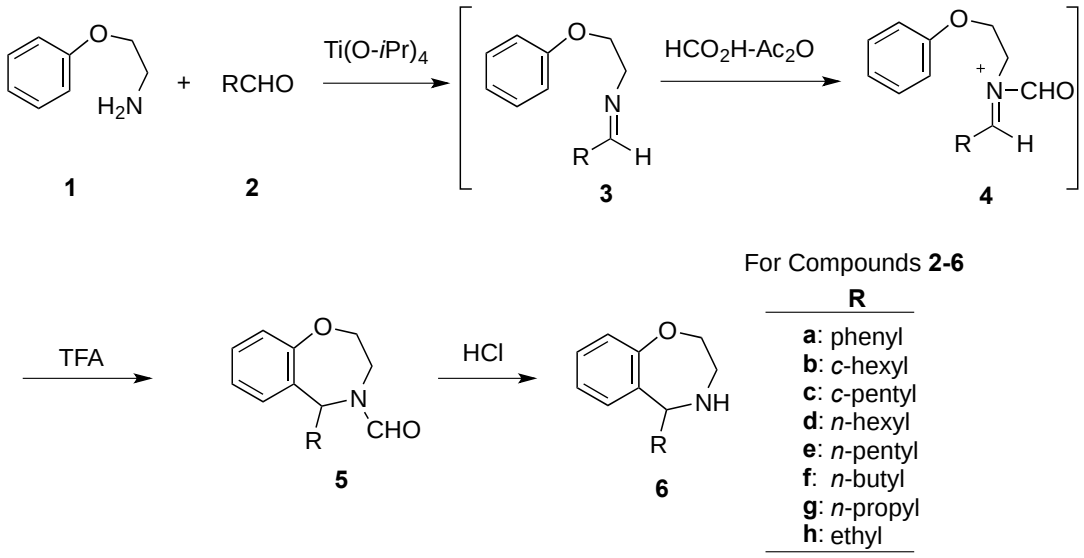
Abstract — 5-Substituted 2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepines (**6**) were synthesized using a modified Pictet-Spengler reaction of formyliminium ion (**4**) as the key step. Cyclization of **4** proceeded readily by using trifluoroacetic acid as a catalyst, giving 5-substituted *N*-formyl- 2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepines (**5**) in 26–78% yield. The imination of 2-phenoxyethanamine (**1**) with aldehydes, formylation of the resulting imines (**3**), and the acid-catalyzed cyclization steps could be carried out in a one-pot procedure. Hydrolysis of **5** with hydrochloric acid gave the 5-substituted 2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepines (**6**) in high yields.

The Pictet-Spengler reaction is one of the key reactions for synthesizing tetrahydroisoquinoline and heteroaryl homologs, which constitute an important class of naturally occurring bioactive substances.[1] The reaction involves acid-catalyzed cyclization of the intermediate imine formed by condensation of the arylethylamine with an aldehyde. We recently improved this key cyclization reaction by substituting *N*-formyliminium ion for the imine. This modified Pictet-Spengler reaction provides a highly efficient and convenient method for synthesizing 1-substituted and 1,1-disubstituted 1,2,3,4-tetrahydroisoqunolines,[2,3] 1,2,3,4-tetrahydro-β-carbolines,[4,5] 1-substituted-2,3-dihydro-1*H*-isoindoles (isoindolines),[6] and 4-substituted and 4,4-disubstituted 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridines.[7] In the synthesis of these compounds, the *N*-formyliminium ion, as anticipated, exhibits stronger electrophilic properties than the

imine. Thus, the modified Pictet-Spengler reaction proceeds under mild acidic conditions, even with substrates in which the aromatic ring lacks electron-donating groups and sterically congested substrates derived from ketones. Furthermore, this method has the added advantage that the overall reactions can be carried out in a one-pot procedure.

In this report, we describe the synthesis of 5-substituted-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepins using the modified Pcitet-Spengler reaction. Benzoxazepines with 7-membered ring systems are known to play crucial roles in a number of biological processes.[8] Benzoxazepines have been synthesized from amides using the Bischler-Napieralski reaction[9,10] or from ketones using an intramolecular imination reaction.[11] However, synthesis of benzoxazepines using the Pictet-Spengler reaction has not been reported. The development of new methods for synthesizing benzoxazepines should contribute not only to heterocyclic chemistry but also to pharmacology.

The modified Pictet-Spengler reaction was carried out in a one-pot procedure, as follows (Scheme 1). The condensation reaction of 2-phenoxyethanamine (**1**) (1.0 mol equiv) and aldehyde (**2**) (1.3 mol equiv) to yield imine (**3**) was carried out in titanium(IV) tetraisopropoxide (1.2 mol equiv) at 70 °C for 2 h without the use of any solvent. Heating the imine (**3**) thus formed *in situ* in a solution containing a large amount of acetic-formic anhydride (50 mol equiv) at 70 °C for 2 h yielded *N*-formyliminium ion (**4**). The reaction mixture of **4** was used as the substrate for the acid-catalyzed cyclization reaction after removal of the excess acetic-formic anhydride by evaporation *in vacuo*.



Scheme 1. Synthesis of 5-substituted 2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepines

When *N*-formyliminium ion (**4a**), which has a phenyl group at the C=N position, was treated with a large excess of trifluoroacetic acid (TFA) (100 mol equiv) at 70 °C for 16 h, the expected cyclization reaction

occurred to give *N*-formyl-5-phenylbenzoxazepine (**5a**) in 78% yield. Similarly, TFA treatment of *N*-formyliminium ions (**4b-h**) with alkyl substituents also induced the cyclization to give benzoxazepines (**5b-h**), respectively, in moderate to low yields. The yield depended on the size of the alkyl substituent; thus, *N*-formyliminium ions with a relatively large alkane, such as cyclohexyl (**4b**), cyclopentyl (**4c**), *n*-hexyl (**4d**), or *n*-pentyl (**4e**), gave products (**5b-e**) in moderate yields (50–70%). By contrast, substrates (**4f-h**), which have small alkyl groups, yielded products (**5f-g**) in low yields (26–36%). The lower yields obtained in the latter cases could be attributed to loss of volatile aldehydes as well as side reactions such as aldol self-condensation, probably in the imination step. The structures of the products were determined using MS, IR, ^{1}H-NMR, and ^{13}C-NMR spectroscopy.[12]

Acidic hydrolysis of *N*-formyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (**5**) afforded 2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (**6**) in excellent yield. The results are summarized in Table 1.[13]

Thus, the modified Pictet-Spengler reaction represents a convenient and highly efficient method for synthesizing various 5-substituted 2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepines, as shown in Table 1. Finally, we wish to note that this is the first reported example of the construction of a 7-membered benzoxazepine ring system using the Pictet-Spengler reaction.

Table 1. Synthesis of 2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (**6**) using the modified Pictet-Spengler reaction

	Modified Pictet-Spenger Reaction							Hydrolysis of **5**	
	N-Formyliminum ion **(4)**		TFA	Conditions		Products		Products	
Run		R	(mol eq.)	Temp (°C)	Time (h)	**5**	Yield (%)	**6**	Yield (%)
1	**4a**	phenyl	100	70	16	**5a**	78	**6a**	93
2	**4b**	*c*-hexyl	100	70	3	**5b**	70	**6b**	95
3	**4c**	*c*-pentyl	100	70	3	**5c**	50	**6c**	76
4	**4d**	*n*-hexyl	100	70	2	**5d**	60	**6d**	91
5	**4e**	*n*-pentyl	100	70	2	**5e**	62	**6e**	78
6	**4f**	*n*-butyl	100	70	2	**5f**	36	**6f**	90
7	**4g**	*n*-propyl	100	70	2	**5g**	35	**6g**	98
8	**4h**	ethyl	100	70	2	**5h**	26	**6h**	89

EXPERIMENTAL

Unless otherwise noted, the following procedures were adopted. Melting points were determined using a

Yanagimoto SP-M1 hot-stage melting point apparatus and are uncorrected. IR spectra were acquired as KBr disks using a HORIBA FT-710 spectrophotometer, and the values are given in cm^{-1}. NMR spectra were acquired using a JEOL JNM-AL 300 (^{1}H-NMR, 300 MHz; ^{13}C-NMR, 75 MHz) NMR spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard, and the chemical shifts are given as δ values. HRFAB-MS spectra were recorded using a JEOL-MS700 spectrometer with glycerol as the matrix. TLC was performed on Merck precoated Silica gel 60 F_{254} plates. Column chromatography was carried out with silica gel (Wakogel C-200). The organic extract from each reaction mixture was washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to dryness.

Modified Pictet-Spengler reaction of 2-phenoxyethanamine (1) and aldehyde (2). General procedure: A mixture of **1** (0.5 g, 3.65 mmol), aldehyde (**2**) (1.2 mol equiv), and Ti(O-*i*Pr)$_4$ (1.2 mol equiv) was heated at 70 °C for 2 h under an argon atmosphere. A solution of acetic-formic anhydride (50 mol equiv) (prepared from HCO_2H [50 mol equiv] and Ac_2O [50 mol equiv]) was added to the reaction mixture at 0 °C, then the mixture was heated at 70 °C for 2 h. After removal of excess acetic-formic anhydride by heating *in vacuo*, CF_3CO_2H (100 mol equiv) was added to the reaction mixture and heated at 70 °C for 2-16 h (as shown in Table 1). The reaction mixture was diluted with MeOH (100 mL) and passed through a short SiO_2 column ($CHCl_3$-MeOH) to remove TiO_2. The eluent was concentrated *in vacuo* to *ca*. 50 mL, and the resulting residue was extracted with $CHCl_3$. After removal of the extraction solvent *in vacuo*, the residue was purified by chromatography over SiO_2 and elution with AcOEt-hexane (1:1-1:3) to give (**5**).

***N*-Formyl-5-phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (5a):** Colorless plates recrystallized from Et_2O, mp 113-115 °C. IR: 1664, 1598, 1577. ^{1}H-NMR: [3.06 (ddd, *J*=15, 10, 3 Hz), 3.53-3.56 (m), 3.77 (ddd, *J*=12, 10, 2 Hz), 4.22-4.30 (m), 4.40-4.45 (m)] (total 4H, C2-H and C3-H,) 5.83, 6.91 (total 1H, each s, C5-H), 7.03-7.36 (9H, m, Ar-H), 8.27, 8.52 (total 1H, each s, -C<u>H</u>O). HR-FABMS *m/z* (MH^+): Calcd for $C_{16}H_{16}NO_2$: 254.1181. Found: 254.1197.

***N*-Formyl-5-cyclohexyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (5b):** Colorless plates from Et_2O. mp 82-84 °C. IR: 1677, 1658, 1644, 1602, 1581. ^{1}H-NMR: 0.83-0.98, 1.10-1.20, 1.65-1.76 (total 10H, each m, cyclohexyl-CH_2), 2.17-2.30 (1H, each m, C1'-H) 3.26-3.35, 3.50-3.73, 3.84-3.95, 4.39-4.46 (total 4H, each m, C2-H and C3-H), 4.56, 5.09 (total 1H, each d, *J*=15, 11, C5-H), 7.00-7.36 (total 4H, m, Ar-H), 8.13, 8.19 (total 1H, each s, C<u>H</u>O). HR-FABMS *m/z* (MH^+): Calcd for $C_{16}H_{22}NO_2$: 260.1651 Found: 260.1662.

***N*-Formyl-5-cyclopentyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (5c):** Yellow gum. IR: 1691, 1666, 1639, 1602, 1579. ^{1}H-NMR: 1.12-1.28, 1.49-1.78 (total 8H, each m, cyclopentyl-CH_2), 2.81-2.91 (1H, m, C1'-H), 3.35-3.45, 3.53-3.72, 3.92-4.02, 4.33-4.77 (total 4H, each m, C2-H and C3-H), 4.56, 5.12 (total 1H, each d, *J*=15, 11, C5-H), 6.99-7.25 (4H, m, Ar-H), 8.10, 8.23 (total 1H, each s, C<u>H</u>O). HR-FABMS

m/z (MH^+): Calcd for $C_{15}H_{20}NO_2$: 246.1494. Found: 246.1490.

***N*-Formyl-5-hexyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (5d):** Yellow oil. IR: 1722, 1693, 1660, 1629, 1604, 1579. ^{1}H-NMR: 0.83-0.87 (3H, m, C6'-H), 1.18-1.28 (8H, m, *n*-hexyl-CH_2), 1.82-1.88 (2H, m, C1'-H), 3.13-3.40, 3.52-3.75, 3.86-3.95, 4.09-4.16, 4.36-4.56, 5.41-5.46 (total 5H, each m, C2-H and C3-H and C5-H), 6.99-7.28 (4H, m, Ar-H), 8.11, 8.23 (total 1H, each s, C<u>H</u>O). HRMS *m/z* (MH^+): Calcd for $C_{16}H_{24}NO_2$: 262.1807. Found: 262.1814.

***N*-Formyl-5-pentyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (5e):** Yellow oil. IR: 1677, 1602, 1577. ^{1}H-NMR: 0.86-0.89 (3H, m, C5'-H), 1.18-1.28 (6H, m, *n*-pentyl), 1.81-1.89, 2.11-2.22 (total 2H, each m, C1'-H), 3.31-3.40, 3.52-3.75, 3.86-3.95, 4.36-4.56, 5.41-5.47 (total 5H, each m, C2-H and C3-H and C5-H), 6.99-7.28 (4H, m, Ar-H), 8.11, 8.23 (total 1H, each s, C<u>H</u>O). HR-FABMS *m/z* (MH^+): Calcd for $C_{15}H_{22}NO_2$: 248.1650. Found: 248.1639.

***N*-Formyl-5-butyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (5f):** Yellow oil. IR: 1687, 1644, 1602, 1577. ^{1}H-NMR: 0.85-0.92 (3H, m, C4'-H), 1.14-1.36 (4H, m, butyl-CH_2), 1.80-1.90, 2.13-2.21 (2H, each m, C1'-H), 3.32-3.40, 3.52-3.75, 3.87-3.95, 4.36-4.56, 5.41-5.47 (total 5H, each m, C2-H and C3-H and C5-H), 6.99-7.28 (4H, m, Ar-H), 8.11-8.23 (total 1H, each s, C<u>H</u>O). HR-FABMS *m/z* (MH^+): Calcd for $C_{14}H_{20}NO_2$: 234.1494. Found: 234.1488.

***N*-Formyl-5-propyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (5g):** Yellow oil. IR: 1687, 1656, 1602, 1577. ^{1}H-NMR: 0.90-0.96 (3H, m, C3'-H), 1.19-1.32 (2H, m, propyl-CH_2), 1.79-1.89, 2.02-2.21 (total 2H, m, C1'-H), 3.32-3.40, 3.52-3.75, 3.86-3.95, 4.38-4.56 5.44-5.49 (total 5H, each m, C2-H and C3-H and C5-H), 6.99-7.28 (4H, m, Ar-H), 8.11, 8.23 (total 1H, each s, C<u>H</u>O). HR-FABMS *m/z* (MH^+): Calcd for $C_{13}H_{18}NO_2$: 220.1339. Found: 220.1352.

***N*-Formyl-5-ethyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (5h):** Yellow oil. IR: 1677, 1602, 1577, 1508. ^{1}H-NMR: 0.83-0.91 (3H, m, CH_3), 1.24-2.21 (2H, m, C1'-H), 3.30-3.38, 3.53-3.90, 4.26-4.57, 5.33-5.38 (total 5H, each m, C2-H and C3-H and C5-H), 6.99-7.27 (4H, m, Ar-H), 8.13, 8.24 (total 1H, each s, C<u>H</u>O). HR-FABMS *m/z* (MH^+): Calcd for $C_{12}H_{16}NO_2$: 206.1181. Found: 206.1177.

Hydrolysis of *N*-formyl -2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (5). General procedure: A solution of (**5**) (100 mg) in EtOH (5 mL) and 10% HCl aqueous solution (5 mL) was refluxed for 3-48 h under an argon atmosphere. The reaction mixture was diluted with water, alkalized with 10% NaOH solution, and extracted with $CHCl_3$. The residue was purified by column chromatography over SiO_2 with MeOH-$CHCl_3$ (9:1) to give (**6**).

5-Phenyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (6a): Reaction time 3 h. Colorless oil. IR: 1602, 1573. ^{1}H-NMR: 3.22-3.25 (2H, m, C3-H), 3.91-3.99, 4.13-4.20 (total 2H, each m, C2-H), 5.22 (1H, s, C5-H), 6.69-6.71, 6.89-6.94, 7.07-7.09, 7.15-7.20, 7.24-7.39 (total 9H, each m, Ar-H). ^{13}C-NMR: 49.2 (C3), 64.5 (C5), 74.1 (C2), 121.4 (Ar or Ph-<u>C</u>H), 123.3 (Ar or Ph-<u>C</u>H), 127.1 (Ar or Ph-<u>C</u>H), 128.0 (Ar or

Ph-CHx2), 128.2 (Ar or Ph-CH), 128.4 (Ar or Ph-CHx2), 129.3 (Ar or Ph-CH), 137.0 (C5a), 141.5 (C1'), 159.5 (C9a). HR-FABMS *m/z* (MH^+): Calcd for $C_{15}H_{16}NO$: 226.1232. Found: 226.1228.

5-Cyclohexyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (6b): Reaction time 3 h. Colorless needles. mp 47-51 °C. IR: 1664, 1581. ^{1}H-NMR: 0.70-1.23, 1.71-1.82, 2.00-2.10 (total 11H, each m, C1'-H and cyclohexyl-CH_2), 2.83 (1H, d, *J*=15 Hz, C3-H), 3.34 (1H, d, *J*=10 Hz, C3-H), 3.33-3.39 (1H, m, C2-H), 3.63 (1H, t, *J*=12 Hz, C2-H), 4.22 (1H, d, *J*=12 Hz, C5-H), 6.86-7.08 (4H, m, Ar-H). ^{13}C-NMR: 26.0 (cyclohexyl-CH_2), 26.1 (cyclohexyl-CH_2), 26.4 (cyclohexyl-CH_2), 30.1 (cyclohexyl-CH_2), 31.5 (cyclohexyl-CH_2), 36.0 (C1'), 45.3 (C3), 67.8 (C5), 74.9 (C2), 121.7 (Ar-CH), 123.0 (Ar-CH), 127.8 (Ar-CH), 130.3 (Ar-CH), 137.1 (C5a), 158.6 (C9a). HR-FABMS *m/z* (MH^+): Calcd for $C_{15}H_{22}NO$: 232.1702. Found: 232.1712.

5-Cyclopentyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (6c): Reaction time 16 h. Yellow oil. IR: 1675, 1600, 1577. ^{1}H-NMR: 1.25-2.00 (8H, m, cyclopentyl-CH_2), 2.62-2.76 (1H, m, C1'-H), 2.99 (1H, ddd, *J*=2.0, 4, 15 Hz, C3-H), 3.47 (1H, ddd, *J*=2, 10, 12, Hz, C3-H), 3.52 (1H, d, *J*=10 Hz, C2-H), 3.78 (1H, ddd, *J*=2, 10, 12 Hz, C2-H), 4.22 (1H, ddd, *J*=3, 4, 12 Hz, C5-H), 6.95-7.17 (4H, m, Ar-H). ^{13}C-NMR: 25.2 (cyclopentyl-CH_2), 25.3 (cyclopentyl-CH_2), 30.1 (cyclopentyl-CH_2), 31.5 (cyclopentyl-CH_2), 40.1 (C'1), 46.3 (C3), 67.3 (C5), 74.8 (C2), 121.5 (Ar-CH), 123.1 (Ar-CH), 127.7 (Ar-CH), 129.1 (Ar-CH), 138.0 (C5a), 158.7 (C9a). HR-FABMS *m/z* (MH^+): Calcd for $C_{14}H_{20}NO$: 218.1545. Found: 218.1553.

5-Hexyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (6d): Reaction time 16 h. Yellow oil. IR: 1677, 1639, 1600, 1577. ^{1}H-NMR: 0.85-0.89 (3H, m, CH_3), 1.28-1.33 (8H, m, hexyl-CH_2), 1.83-1.92 (2H, m, C1'-H), 3.05 (1H, ddd, *J*=2, 5, 7 Hz, C3-H), 3.39 (1H, ddd, *J*=2, 8, 11 Hz, C3-H), 3.85 (1H, t , *J*=8 Hz, C2-H), 3.86 (1H, ddd, *J*=2, 8, 12 Hz, C2-H), 4.13 (1H, ddd, *J*=3, 5, 8 Hz, C5-H), 6.97-7.18 (4H, m, Ar-H). ^{13}C-NMR: 14.0 (CH_3), 22.6 (hexyl-CH_2), 26.8 (hexyl-CH_2), 29.2 (hexyl-CH_2), 31.7 (hexyl-CH_2), 32.3 (hexyl-CH_2), 46.9 (C3), 61.1 (C5), 75.0 (C2), 121.6 (Ar-CH), 123.3 (Ar-CH), 127.8 (Ar-CH), 128.1 (Ar-CH), 138.4 (C5a), 159.0 (C9a). HR-FABMS *m/z* (MH^+): Calcd for $C_{15}H_{24}NO$: 234.1858. Found: 234.1850.

5-Pentyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (6e): Reaction time 16 h. Yellow oil. IR: 1639, 1600, 1577. ^{1}H-NMR: 0.85-0.90 (3H, m, CH_3), 1.30-1.43 (6H, m, pentyl-CH_2), 1.82-1.92 (2H, m, C1'-H), 3.06 (1H, ddd, *J*=2, 5, 8 Hz, C3-H), 3.39 (1H, ddd, *J*=3, 8, 11 Hz, C3-H), 3.84-3.91 (2H, m, C2-H), 4.12 (1H, ddd, *J*=3, 6, 8 Hz, C5-H), 6.97-7.18 (4H, m, Ar-H). ^{13}C-NMR: 13.9 (CH_3), 22.5 (pentyl-CH_2), 26.5 (pentyl-CH_2), 31.7 (pentyl-CH_2), 32.3 (pentyl-CH_2), 46.9 (C3), 61.1 (C5), 75.0 (C2), 121.5 (Ar-CH), 123.3 (Ar-CH), 127.7 (Ar-CH), 128.1 (Ar-CH), 138.4 (C5a), 159.0 (C9a). HR-FABMS *m/z* (MH^+): Calcd for $C_{14}H_{22}NO$: 220.1702. Found: 220.1705.

5-Butyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (6f): Reaction time 48 h. Yellow oil. IR: 1675, 1600, 1577. ^{1}H-NMR: 0.88-0.93 (3H, m, CH_3), 1.24-1.44 (4H, m, butyl-CH_2), 1.84-1.90 (2H, m, C1'-H), 3.06

(1H, ddd, *J*=2, 5, 7 Hz, C3-H), 3.40 (1H, ddd, *J* =2, 5, 7 Hz, C3-H), 3.84-3.91 (2H, m, C2-H), 4.13 (1H, ddd, *J* =2, 5, 7 Hz, C5-H), 6.98-7.18 (4H, m, Ar-H). ^{13}C-NMR: 14.0 ($\underline{C}H_3$), 22.6 (butyl-$\underline{C}H_2$), 29.1 (butyl-$\underline{C}H_2$), 32.1 (butyl-$\underline{C}H_2$), 47.0 (C3), 61.2 (C5), 75.1 (C2), 121.6 (Ar-$\underline{C}H$), 123.4 (Ar-$\underline{C}H$), 127.8 (Ar-$\underline{C}H$), 128.2 (Ar-$\underline{C}H$), 138.4 (C5a), 159.1 (C9a). HR-FABMS *m/z* (MH^+): Calcd for $C_{13}H_{20}NO$: 206.1545. Found: 206.1551.

5-Propyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (6g): Reaction time 3 h. Yellow oil. IR: 1675, 1600, 1579. ^{1}H-NMR: 0.92-0.97 (3H, m, CH_3), 1.26-1.31 (1H, m, propyl-CH_2), 1.41-1.48 (1H, m, propyl-CH_2), 1.83-1.90 (2H, m, C1'-H), 3.03-3.09 (1H, m, C3-H) 3.37-3.43 (1H, m, C3-H), 3.84-3.91 (2H, m, C2-H), 4.06-4.16 (1H, m, C5-H), 6.93-7.17 (4H, m, Ar-H). ^{13}C-NMR: 13.9 ($\underline{C}H_3$), 20.0 (propyl-$\underline{C}H_2$), 34.5 (propyl-$\underline{C}H_2$), 46.9 (C3), 60.8 (C5), 75.0 (C2), 121.6 (Ar-$\underline{C}H$), 123.3 (Ar-$\underline{C}H$), 127.8 (Ar-$\underline{C}H$), 128.2 (Ar-$\underline{C}H$), 138.3 (C5a), 159.0 (C9a). HR-FABMS: Calcd for $C_{12}H_{18}NO$: 192.1388. Found: 192.1395.

5-Ethyl-2,3,4,5-tetrahydrobenzo[*f*][1,4]oxazepine (6h): Reaction time 48 h. Yellow oil. IR: 1602, 1577. ^{1}H-NMR: 0.95 (3H, t, *J*=7 Hz, CH_3), 1.92 (2H, quint, *J*=7 Hz, CH_2), 3.06 (1H, ddd, *J*=2, 5, 7 Hz, C3-H), 3.39 (1H, ddd, *J*=2, 8, 11 Hz, C3-H), 3.77 (1H, t, *J*=7 Hz, C5-H), 3.87 (1H, ddd, *J*=2, 8, 11 Hz, C2-H), 4.13 (1H, ddd, *J*=3, 5, 8 Hz, C2-H), 6.92-7.24 (4H, m, Ar-H). ^{13}C-NMR: 11.4 ($\underline{C}H_3$), 25.3 ($\underline{C}H_2$), 46.8 (C3), 62.8 (C5), 74.9 (C2), 121.6 (Ar-$\underline{C}H$), 123.3 (Ar-$\underline{C}H$), 127.8 (Ar-$\underline{C}H$), 128.3 (Ar-$\underline{C}H$), 138.0 (C5a), 159.0 (C9a). HR-FABMS: Calcd for $C_{11}H_{16}NO$: 178.1232. Found: 178.1229.

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12. The ^{1}H- and ^{13}C-NMR spectra of *N*-formyl compounds (**5**) exhibited complex signals attributable to rotational isomerism of the N-CO bond. Therefore, ^{13}C-NMR spectra of cyclized products were assigned based on measurements of *N*-deformyl derivatives (**6**).
13. In this modified Pictet-Spengler reaction, unstable intermediate imine (**3**) and *N*-formylimimium ion (**4**) were not isolated. The yield of cyclization products (**5**) was calculated from starting material amine (**1**).