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Synthesis of tetrahydroisoquinolines and isochromans via Pictet–Spengler reactions catalyzed by Brønsted acid–surfactant-combined catalyst in aqueous media

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Abstract—Perfluorooctanesulfonic acid (PFOSA), Brønsted acid–surfactant-combined catalyst, efficiently catalyzes the Pictet–Spengler reactions of β-arylethyl carbamate derivatives with aldehydes in water. The present reaction is accelerated by the addition of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). PFOSA in HFIP–water (10 v/v %) is also successfully applied to the oxa-Pictet–Spengler reactions of β-arylethyl alcohol compounds.
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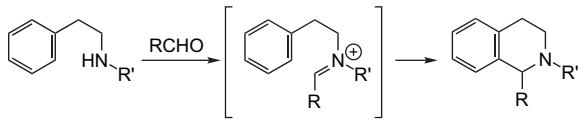
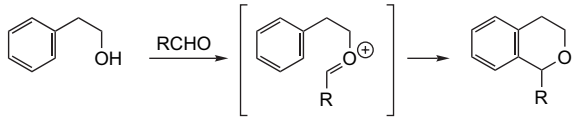
1. Introduction

The Pictet–Spengler reaction was reported for the first time in 1911,[1] and the reaction became a powerful methodology for preparing tetrahydroisoquinoline and indole molecules.[2,3] The Pictet–Spengler reaction takes part in the cyclization of imines or iminium ions formed by dehydration reaction of β-arylethyl amine derivatives with aldehydes (Scheme 1). In organic solvent, the catalytic reactions of tryptamine and *m*-tyramine have been achieved by the use of Brønsted acid,[4] Lewis acid,[5] or organocatalyst,[6] while less reactive β-phenethylamine derivative requires a large excess of the strong Brønsted acid. Recently, it has been reported that a zeolite-type adsorbent, which can be recycled, efficiently catalyzed the Pictet–Spengler reactions of less reactive β-phenethylamine derivative in ethanol.[7] Although the reactions in water or aqueous media have been known, they require large excess of strong Brønsted acid and/or have the limitation in reactants.[8]



Scheme 1.

Oxa-Pictet–Spengler reaction is a variation of the Pictet–Spengler reaction, and thus isochroman compounds can be obtained from β-arylethyl alcohol derivatives with aldehydes (Scheme 2).[9,10] Although some catalytic reactions have been developed,[11] to our knowledge, these examples have been limited to the reaction in nonaqueous media.[12]



Scheme 2.

Recently, a variety of organic reactions in water or aqueous media have been studied from the viewpoint of green chemistry, and have been received attention in the light of unique physical and chemical properties of water.[13] In the commonly reported aqueous reactions, Brønsted acid–surfactant-combined catalyst (BASC) has been known to play an important role not only for the activation of the substrate but also for the solubilization of organic substrates by the formation of colloidal dispersions. In addition, it is noteworthy that BASC works well for dehydration reactions such as the esterification and etherification in water as well as three-component Mannich reactions and aza Diels–Alder reactions including dehydrative formation of imine derivatives.[14,15,16] The efficiency of BASC for dehydration reactions in water encouraged us to examine the Pictet–Spengler reactions in water, and we reported in a communication that perfluorooctanesulfonic acid (PFOSA) as BASC efficiently catalyzes the Pictet–Spengler reactions of β-arylethyl carbamate

Keywords: Surfactant; Brønsted acid; Pictet–Spengler reaction; Isoquinoline; Isochroman.
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derivatives with aldehydes in water.[17] Interestingly, these reactions in water were found to be accelerated by the addition of 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP). Further study using various substrates revealed the efficiency of PFOSA–HFIP system for the oxa-Pictet–Spengler reaction of β-arylethyl alcohols in water. In this paper, we describe the mild and facile Pictet–Spengler reaction and its oxygen version.

2. Results and discussion

2.1. Pictet–Spengler reaction in water

At the outset, we focused our initial efforts on the screening of Brønsted acid catalysts for the Pictet–Spengler reaction of carbamate **1** with *n*-heptanal in water at room temperature (Table 1). Carbamate **1** was expected to form a reactive *N*-acyl iminium intermediate,[18,19] while the use of 1 equiv hydrochloric or sulfuric acid ended with the recovery of **1** (entries 1 and 2).[20] Although Brønsted acids such as trifluoroacetic acid (TFA), *p*-toluenesulfonic acid (TsOH), and trifluoromethanesulfonic acid (TfOH) have been reported to be good catalysts for the Pictet–Spengler reactions in organic solvents,[19,21] they were ineffective catalysts in water (entries 3–5). On the other hand, the use of *n*-dodecylbenzenesulfonic acid (DBSA), which is known as BASC,[14] or a combination of Brønsted acid and sodium dodecyl sulfate (SDS)[15] slightly increased the yield of **2a** (entries 6 and 7). Notably, perfluoroalkanesulfonic acids such as perfluorobutanesulfonic acid (PFBSA, entry 8) and PFOSA[22,23] accelerated the reactions of **1**, and 20 mol % PFOSA brought about **2a** in 90% yield at room temperature for 18 h (entry 9).[24]

Since an addition of alcohol to aqueous surfactant has been known to show changes in properties of surfactant,[25] we investigated the additive effect of alcohol (3 equiv to substrate) in the reaction of **1** with *n*-heptanal (1.2 equiv) in the presence of PFOSA (20 mol %) at room temperature for 4 h (Fig. 1). Compared with hydrocarbon alcohols, the fluorinated alcohol, in particular, 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) exerted a marked effect on the formation of **2a**. Thus, in the presence of HFIP, **1** was consumed at room temperature within 4 h to give **2a** in 99% yield, in which the concentration of HFIP in water corresponds to 11.5 v/v % (entry 10, Table 1). HFIP showed its efficiency for the use of DBSA as well (entry 14), while the reaction with fluorinated alkanesulfonic acids such as PFBSA and TfOH were slightly accelerated (entries 11 and 12). The sole use of HFIP did not yield **2a** in the absence of catalyst (entry 14). These results indicate that hydrophobicities of

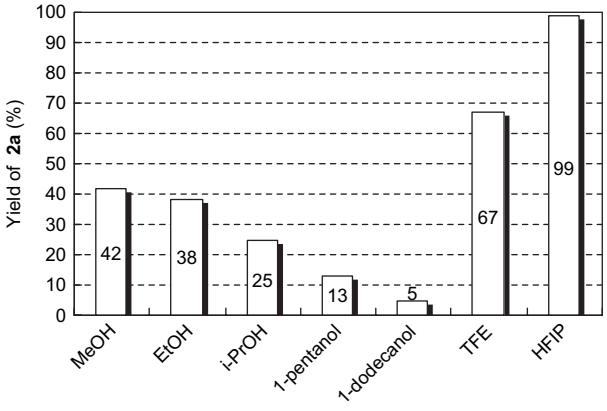
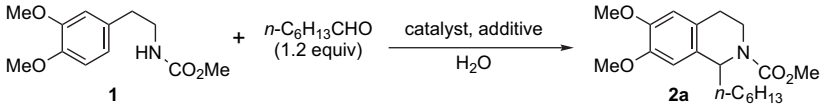


Figure 1. Additive effect of alcohol (3 equiv to **1**) in the PFOSA (20 mol %)-catalyzed reaction of **1** with *n*-heptanal (1.2 equiv) at rt for 4 h in water (1 mL). (Yield of **2a** was determined by ^{1}H NMR. TFE: 2,2,2-trifluoroethanol; HFIP: 1,1,1,3,3,3-hexafluoro-2-propanol.)

Table 1. Screening of Brønsted acid catalysts for the Pictet–Spengler reaction in water[a]



Entry	Catalyst[b] (mol %)	Additive[b] (equiv)	Temperature (°C)	Time (h)	Yield of **2a**[c] (%)	Yield of **1**[c] (%)
1	HCl (100)		rt	18	—	99
2	H_2SO_4 (100)	—	rt	18	—	99
3	TFA (20)	—	rt	18	—	99
4	TsOH (20)	—	rt	18	2	97
5	TfOH (20)	—	rt	18	4	92
6	TfOH (20)	SDS (0.2)	rt	18	11	89
7	DBSA (20)	—	rt	18	27	69
8	PFBSA (20)	—	rt	18	61	36
9	PFOSA (20)	—	rt	18	90 (84)	—
10	PFOSA (20)	HFIP (3)	rt	4	99 (97)	—
11	PFBSA (20)	HFIP (3)	rt	4	80	18
12	TfOH (20)	HFIP (3)	rt	4	21	75
13	—	HFIP (3)	rt	4	—	99
14	DBSA (20)	HFIP (3)	rt	4	99 (95)	—
15	DBSA (20)	*i*-PrOH (3)	rt	4	14	85
16[d]	PFOSA (20)	HFIP (3)	rt	1.5	99 (96)	—
17	PFOSA (10)	HFIP (3)	rt	24	99 (97)	—
18	PFOSA (5)	HFIP (3)	60	24	99 (99)	—

[a] Reaction concentration: **1**/water=0.42 mmol/1 mL.
[b] Equivalent to **1**.
[c] Yield was determined by ^{1}H NMR with toluene as an internal standard, and yield in parentheses was isolated yield.
[d] Neat condition.

catalysts are important for the reaction in HFIP–water. On the other hand, the addition of *i*-PrOH was inferior to that of HFIP even in the reaction with hydrocarbon surfactant (entry 14 vs 15).[26] Although it is considered that the additive effect of HFIP takes part in the enhancement of acidity of catalyst, there are no marked differences in pH for each catalyst (PFOSA, DBSA, or TfOH) solution in HFIP–water.[27]

It should be mentioned that HFIP–water concentration profile in Figure 2 leads to 10–20 v/v % as the optimum concentration for PFOSA-catalyzed reaction of **1** with *n*-heptanal. Although the reaction of **1** with 3 equiv HFIP under the neat condition (entry 16, Table 1) was faster than that in water, the yield of **2a** at the endpoint was unchanged. Thus, it is obvious that HFIP is an useful adjunct to PFOSA during the formation of **2a** in water. The use of less amount of PFOSA (5 or 10 mol %) as a catalyst in HFIP–H_2O required a prolonged reaction time and higher temperature to afford product **2a** in excellent yield (entries 17 and 18, Table 1).

The present catalytic Pictet–Spengler reaction of carbamate **1** in water was applied to various aldehydes as shown in Table 2. Regardless of hydrophobicities of aldehydes, many aldehydes successfully reacted with carbamate **1** by PFOSA in water or in HFIP–water, and the corresponding cyclized products were obtained in high yields in most cases. The use of *t*-BuCHO or ketone compounds (acetone or acetophenone), however, gave no cyclized product along with recovery of **1**. In both reactions in water and in HFIP–water, water-soluble aldehydes (R=Et, H, *i*-Pr) showed inferior reactivities to that of water-insoluble aldehydes (R=*n*-hexyl, *n*-dodecyl, *c*-hexyl). A similar observation has been reported in the DBSA-catalyzed esterification of carboxylic acids with alcohols in water.[14b] It has been suggested that hydrophobic substrates readily assemble together with DBSA through hydrophobic interactions to form emulsion droplets and the hydrophobicity of substrates as well as DBSA facilitates the dehydration in water.[14b] In the present reaction, hydrophobic substrates and PFOSA in the absence of HFIP would be considered to form an analogous hydrophobic area enough to exclude water molecules. Although the role of HFIP is unclear,[28,29] the hydrophobic fluorinated alcohol might have a beneficial effect for the aggregation of substrates and PFOSA in water.

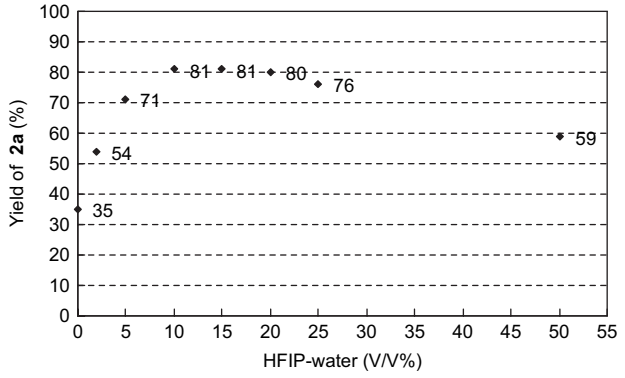


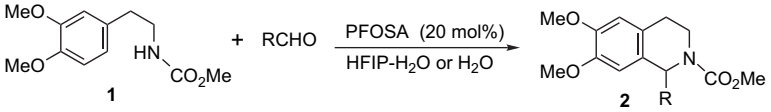
Figure 2. HFIP–water concentration profile for the PFOSA (20 mol %)-catalyzed reaction of **1** with *n*-heptanal (1.2 equiv) in solvent (1 mL) at rt for 1.5 h. (Yield of **2a** was determined by ^{1}H NMR.)

We next examined the effect of substituent on the aromatic ring (Table 3). When *m*-tyramine derivative **3** was used, the reactions with both *n*-heptanal and benzaldehyde proceeded smoothly, and the corresponding *para*-cyclized products **4a** and **4e** were obtained as a major isomer, respectively (entries 3 and 4). Likewise, 3-MeO substituted derivative **5** afforded good results (entries 5 and 6). On the other hand, carbamate **7**, which has no activating substituent, did not bring about the cyclization reaction (entries 7 and 8).

2.2. Oxa-Pictet–Spengler reaction in water

The established efficiency of the PFOSA in HFIP–water for the catalytic Pictet–Spengler reaction of β-arylethyl carbamate derivatives encouraged us to examine the oxa-Pictet–Spengler reaction of β-arylethyl alcohol **9** (Scheme 3). In the reported oxa-Pictet–Spengler reactions in organic

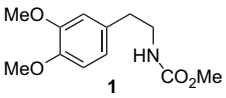
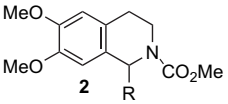
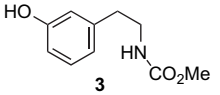
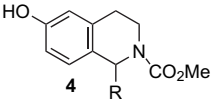
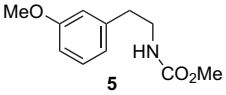
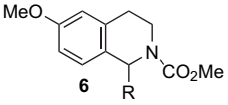
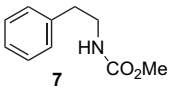
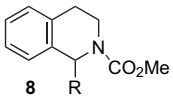
Table 2. Catalytic Pictet–Spengler reactions of **1** with various aldehydes



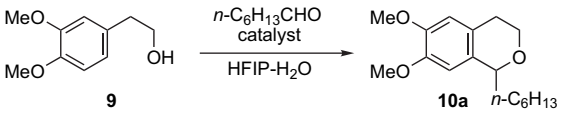
Aldehyde (equiv)	Reaction in HFIP–water[a]			Reaction in water[b]		
	Temperature (°C)	Time (h)	**2** (%)[c]	Temperature (°C)	Time (h)	**2** (%)[c]
n-C_6H_{13}CHO (1.2)	rt	4	**2a** (97)	rt	18	**2a** (84)
n-$C_{11}H_{23}$CHO (1.2)	rt	4	**2b** (90)	60	18	**2b** (92)
EtCHO (1.2)	rt	10	**2c** (95)	60	5	**2c** (99)[d]
37% Formaline (1.2)	rt	8	**2d** (86)	60	2	**2d** (93)
PhCHO (1.2)	90	19	**2e** (94)	90	18	**2e** (81)[e]
c-C_6H_{11}CHO (1.8)	90	4	**2f** (99)			
i-PrCHO (1.8)	90	20	**2g** (96)			
t-BuCHO (2.5)	90	18	**2h** (—)[f]			

[a] Reaction concentration: **1**/HFIP/water=0.42 mmol/130 μL/1 mL.
[b] Reaction concentration: **1**/water=0.42 mmol/1 mL.
[c] Isolated yield.
[d] Aldehyde: 2.5 equiv.
[e] PFOSA: 1.2 equiv.
[f] Recovery of **1**: 99%.

Table 3. Catalytic Pictet–Spengler reactions of various carbamates[a]

Entry	Carbamate	Aldehyde	Condition		Product	Yield (%)[b]
			Temperature (°C)	Time (h)		
1	 **1**	*n*-C_6H_{13}CHO	rt	4	 **2** R	**2a**: R=*n*-C_6H_{13} 97
2		PhCHO	90	19		**2e**: R=Ph 94
3	 **3**	*n*-C_6H_{13}CHO	rt	4	 **4** R	**4a**: R=*n*-C_6H_{13} 90 (7.6:1)[c]
4		PhCHO	90	18		**4e**: R=Ph 84 (16:1)[c]
5	 **5**	*n*-C_6H_{13}CHO	rt	10	 **6** R	**6a**: R=*n*-C_6H_{13} 95 (14:1)[c]
6		PhCHO	90	5		**6e**: R=Ph 99 (16:1)[c]
7	 **7**	*n*-C_6H_{13}CHO	90	20	 **8** R	**8a**: R=*n*-C_6H_{13} —[d]
8		PhCHO	90	15		**8e**: R=Ph —[d]

[a] All Reactions of carbamates (0.42 mmol) with aldehyde (1.2 equiv) were carried out in the presence of PFOSA (20 mol %) in HFIP–water (130 μL/1 mL).
[b] Isolated yield.
[c] Regioisomer ratio (*para*/*ortho* cyclized product).
[d] Recovery of **7**: 98%.



Scheme 3.

solvent, Brønsted acid such as TsOH in the presence of dehydrating reagent (Na_2SO_4 and molecular sieves) has been known to be an efficient catalyst.[11a,b] TsOH of 10 mol %, however, turns out to be inefficient for the reaction of alcohol **9** with *n*-heptanal (1.2 equiv) in HFIP–water (10 v/v %) at room temperature (Fig. 3). On the other hand, PFOSA exerted a remarkable effect in the reaction of **9**, and the product **10a** was obtained in 34% yield at room temperature for 2 h along with recovery of **9** in 58% (Fig. 3). It also turns out that HFIP–water concentration profile in Figure 4 showed 10 v/v % as the optimum concentration for PFOSA-catalyzed reaction of **9** with *n*-heptanal.

Under the optimized conditions, scope of the PFOSA-catalyzed oxa-Pictet–Spengler reactions in HFIP–water

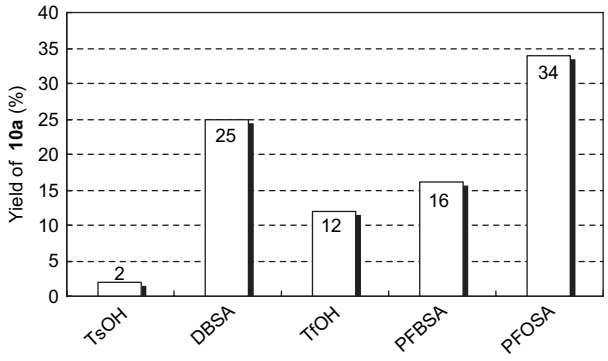


Figure 3. Catalysts (10 mol % to **9**) for the reaction of **9** with *n*-heptanal (1.2 equiv) at rt for 2 h in HFIP–water (10 v/v %, 1 mL). (Yield of **10a** was determined by ^{1}H NMR.)

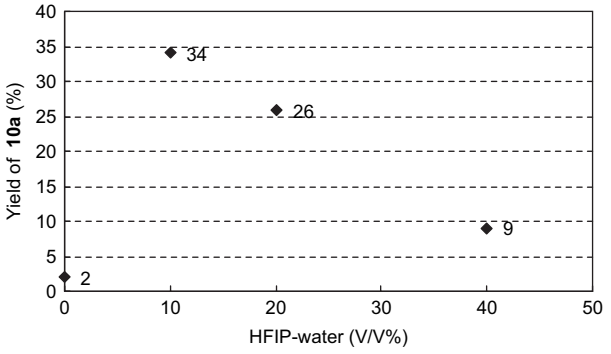


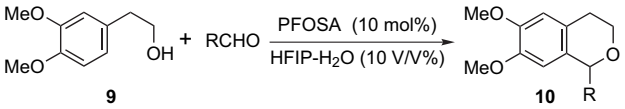
Figure 4. HFIP–water concentration profile for the PFOSA (10 mol %)-catalyzed reaction of **9** with *n*-heptanal (1.2 equiv) in solvent (1 mL) at rt for 2 h. (Yield of **10a** was determined by ^{1}H NMR.)

(10 v/v %) was examined (Tables 4 and 5). By use of 10 mol % PFOSA, the reaction of alcohol **9** with *n*-heptanal completed at room temperature for 48 h giving rise to **10a** in 93% yield (entry 1, Table 4). PFOSA (10–20 mol %) in HFIP–water could be applied to oxa-Pictet–Spengler reactions of **9** with other aldehydes and the desirable products were obtained in good yields (entries 2–7). As in the reactions of carbamates (vide ante), water-soluble aldehydes (R=Et, H, *i*-Pr) showed the poor reactivity to that of water-insoluble aldehydes (R=*n*-hexyl, *n*-dodecyl, *c*-hexyl). As shown in Table 5, 3-MeO substituted derivative **11** reacted smoothly with both *n*-heptanal and benzaldehyde to give the corresponding *para*-cyclized products **12a** and **12e** in high yields as a single isomer, respectively (entries 1 and 2). Phenethyl alcohol **13**, however, afforded no cyclized products (entries 3 and 4).

2.3. Pictet–Spengler reaction versus intermolecular Friedel–Crafts reaction

In the mechanistic points, the formation of tetrahydroisoquinoline or isochroman compounds under the present

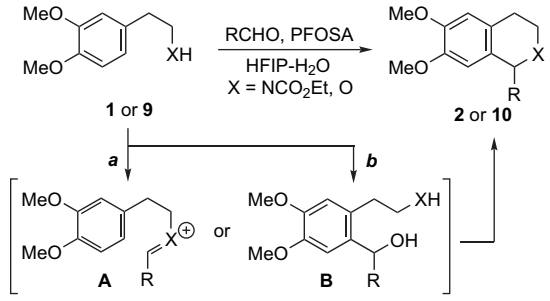
Table 4. Catalytic oxa-Pictet–Spengler reactions of **9** with various aldehydes[a]



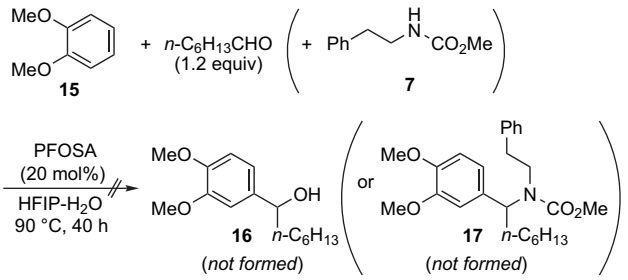
Entry	Aldehyde (equiv)	Temperature (°C)	Time (h)	**10** (%)[b]
1	*n*-C_6H_{13}CHO (1.2)	rt	48	**10a** (93)
2	*n*-$C_{11}H_{23}$CHO (1.8)	rt	48	**10b** (91)
3	EtCHO (1.8)	rt	96	**10c** (87)
4[c]	37% Formaline (3.6)	60	72	**10d** (86)
5	PhCHO (2.4)	90	18	**10e** (95)
6[c]	*c*-C_6H_{11}CHO (4.8)	90	4	**10f** (84)
7[c]	*i*-PrCHO (4.8)	90	24	**10g** (60)

[a] Reaction concentration: **1**/HFIP–water=0.42 mmol/1 mL.
[b] Isolated yield.
[c] PFOSA: 20 mol %.

condition would be possible to proceed through the intermolecular Friedel–Crafts type reaction of aryl core of substrate with aldehyde (path **b**, Scheme 4) prior to the generation of *N*-acyl iminium or oxonium ion intermediate **A** as we expected (path **a**). To gain a better understanding, we attempted the reaction of 3,4-dimethoxybenzene **15** with *n*-heptanal (Scheme 5). Under similar condition to **2a** (entry 6, Table 1), the presumed product **16** was not obtained even at 90 °C for 40 h. The three-component coupling reaction of **15**, *n*-heptanal, and carbamate **7** did not afford the product **17** either, but recovered compound **15** (Scheme 5). By taking into consideration of *N*-acyl iminium ion-activated Pictet–Spengler or Mannich reaction[18] and oxa-Pictet–Spengler reaction[9], we believe that the present process involves *N*-acyl iminium or oxonium intermediate **A** as shown in Scheme 4.



Scheme 4.



Scheme 5.

3. Conclusion

For the purpose of the catalytic Pictet–Spengler reactions of β-arylethyl carbamate derivatives in water, PFOSA was found to be efficient. It was also found that the addition of HFIP to water significantly accelerates the catalytic reactions with various aldehydes. PFOSA in 10 v/v % HFIP–water systems was applied to the oxa-Pictet–Spengler reactions of β-arylethyl alcohol compounds with various aldehydes. We believe that the present method could be contributed to the syntheses of tetrahydroisoquinoline and isochroman compounds from the standpoint of the reduction of organic solvent.

4. Experimental

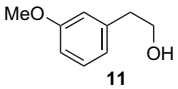
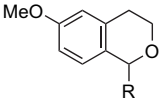
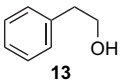
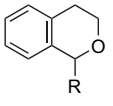
4.1. General

Carbamates **1**, **3**, **5**, and **7** were prepared by the reported procedure in literatures.[30] Substrates **9**, **11**, and **13** are commercially available. Column chromatography was performed on silica gel (63–200 μm mesh, spherical, neutral). ^{1}H and ^{13}C NMR spectra were measured at 300.4 and 75.5 MHz in $CDCl_3$, respectively, and the chemical shifts are given in parts per million using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^{1}H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR as an internal standard. From NMR spectra of tetraisoquinoline compounds **2**, **4**, and **6**, each ca. 1:1 rotamer mixture was observed. Mass spectra and HRMS were recorded by FAB method.

4.2. Screening of Brønsted acid catalyst for Pictet–Spengler reaction in water

To a mixture of carbamate **1** (0.42 mmol) and Brønsted acid (0.084 or 0.42 mmol) in water (1.0 mL) was added

Table 5. Catalytic oxa-Pictet–Spengler reactions of some carbamates[a]

Entry	Carbamate	Aldehyde (equiv)	Temperature (°C)	Time (h)	Product	Yield[b] (%)
1		$CH_3(CH_2)_5CHO$ (1.2)	rt	48	 **12a**: R=$CH_3(CH_2)_5$	93
2	**11**	PhCHO (2.4)	90	18	**12e**: R=Ph	86
3		$CH_3(CH_2)_5CHO$ (1.2)	90	20	 **14a**: R=$CH_3(CH_2)_5$	—[c]
4	**13**	PhCHO (2.4)	90	15	**14e**: R=Ph	—[c]

[a] All Reactions of carbamates (0.42 mmol) with aldehyde (1.2 equiv) were carried out in the presence of PFOSA (10 mol %) in HFIP–water (10 v/v %, 1 mL).
[b] Isolated yield.
[c] Phenethyl alcohol **13** was recovered.

n-heptanal (0.50 mmol). After being stirred at ambient temperature for 18 h, the reaction mixture was quenched with saturated aq $NaHCO_3$ and brine, and extracted with ether. The organic layer was dried over $MgSO_4$, and the filtrate was concentrated to dryness to give a crude mixture. The ratio of **2a/1** and the yield of **2a** were determined by ^1H NMR using toluene (50 μL, 0.47 mmol) as an internal standard.

4.3. General procedure for PFOSA-catalyzed Pictet–Spengler reactions in HFIP–water

To a mixture of carbamate **1**, **3**, **5**, or **7** (0.42 mmol), perfluorooctanesulfonic acid (PFOSA, 0.084 mmol), and hexafluoroisopropanol (HFIP, 1.3 mmol) in water (1.0 mL) was added aldehyde (0.50–1.0 mmol). After being stirred until the consumption of starting carbamate by TLC analysis, the reaction mixture was quenched with saturated aq $NaHCO_3$ and brine, and extracted with ether. The organic layer was dried over $MgSO_4$, and the filtrate was concentrated to dryness to give a crude mixture. Purification by silica gel column chromatography (hexane/AcOEt=6:1) gave a pure product **2**, **4**, or **6**.

4.3.1. *N*-(Methoxycarbonyl)-6,7-dimethyloxy-1-hexyl-1,2,3,4-tetrahydroisoquinoline (2a). Colorless crystals. Mp 56–57 °C. IR (KBr) ν cm^{-1}: 1658, 1259. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.72–0.89 (3H, m), 1.01–1.48 (8H, m), 1.53–1.79 (2H, m), 2.55 (1H, dt, J=15.9, 3.5 Hz), 2.69–2.90 (1H, m), 3.04–3.29 (1H, m), 3.64 (3H, s), 3.76 (3H, s), 3.78 (3H, s), 3.88–4.02 (0.5H, m), 4.09–4.22 (0.5H, m), 4.90 (0.5H, dd, J=9.2, 4.1 Hz), 5.02 (0.5H, dd, J=8.1, 5.0 Hz), 6.44–6.53 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0, 22.6, 26.2, 26.2, 28.0, 29.1, 29.2, 31.7, 36.7, 36.8, 37.2, 37.9, 52.5, 54.3, 54.5, 55.8, 56.0, 109.8, 110.1, 111.4, 111.5, 125.6, 125.9, 129.9, 130.3, 147.3, 147.6, 156.2. FAB-LM *m/z*: 336 (M+H). FAB-HM Calcd for $C_{19}H_{30}NO_4$: 336.2179. Found: 336.2175. Anal. Calcd for $C_{19}H_{29}NO_4$: C, 67.74; H, 8.76; N, 4.09. Found: C, 68.03; H, 8.71; N, 4.18.

4.3.2. *N*-(Methoxycarbonyl)-6,7-dimethyloxy-1-undecyl-1,2,3,4-tetrahydroisoquinoline (2b). Colorless crystals. Mp 41–42 °C. IR (KBr) ν cm^{-1}: 1701, 1257. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.86 (3H, t, J=6.9 Hz), 1.16–1.52 (18H, m), 1.59–1.84 (2H, m), 2.60 (1H, dt, J=15.9, 3.5 Hz), 2.74–2.86 (1H, m), 3.10–3.32 (1H, m), 3.70 (3H, s), 3.82 (3H, s), 3.83 (3H, s), 3.91–4.08 (0.5H, m), 4.14–4.30 (0.5H, m), 4.91–5.02 (0.5H, m), 5.02–5.14 (0.5H, m), 6.49–6.60 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0, 22.6, 26.2, 27.7, 28.0, 29.2, 29.4, 29.5, 29.6, 31.8, 36.6, 36.8, 37.2, 37.9, 52.4, 54.3, 54.4, 55.8, 55.9, 109.8, 110.1, 111.3, 111.5, 125.6, 125.9, 129.8, 130.2, 147.3, 147.6. FAB-LM *m/z*: 406 (M+H). FAB-HM Calcd for $C_{24}H_{40}NO_4$: 406.2949. Found: 406.2958. Anal. Calcd for $C_{24}H_{39}NO_4$: C, 71.07; H, 9.69; N, 3.45. Found: C, 71.47; H, 9.44; N, 3.24.

4.3.3. *N*-(Methoxycarbonyl)-6,7-dimethyloxy-1-ethyl-1,2,3,4-tetrahydroisoquinoline (2c). Colorless crystals. Mp 71–72 °C. IR (KBr) ν cm^{-1}: 1697, 1263. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.94 (3H, t, J=6.7 Hz), 1.69–1.82 (2H, m), 2.60 (1H, dt, J=15.9, 3.7 Hz), 2.73–2.92 (1H, m), 3.08–3.31 (1H, m), 3.69 (3H, s), 3.81 (3H, s), 3.82 (3H, s), 3.90–4.07 (0.5H, m), 4.13–4.28 (0.5H, m), 4.88 (0.5H, t, J=6.8 Hz), 5.00 (0.5H, t, J=6.8 Hz), 6.56 (2H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 10.8, 27.7, 28.0, 29.4, 29.6, 37.3, 37.9, 52.4, 55.6, 55.8, 55.9, 109.8, 110.1, 111.3, 111.4, 125.6, 125.9, 129.6, 129.9, 147.2, 147.5, 156.3. FAB-LM *m/z*: 280 (M+H). FAB-HM Calcd for $C_{15}H_{21}NO_4$: 280.1579. Found: 280.1579. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.59; H, 7.57; N, 4.87. Found: C, 64.50; H, 7.58; N, 5.01.

4.3.4. *N*-(Methoxycarbonyl)-6,7-dimethyloxy-1,2,3,4-tetrahydroisoquinoline (2d). The ^1H NMR spectra of **2d** were identical to that reported in the literature.[31]

4.3.5. *N*-(Methoxycarbonyl)-6,7-dimethyloxy-1-phenyl-1,2,3,4-tetrahydroisoquinoline (2e). The ^1H NMR spectra of **2e** were identical to that reported in the literature.[19]

4.3.6. *N*-(Methoxycarbonyl)-1-cyclohexyl-6,7-dimethyloxy-1,2,3,4-tetrahydroisoquinoline (2f). Pale yellow oil. IR (neat) ν cm^{-1}: 1697, 1255. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.92–1.25 (5H, m), 1.49–1.81 (6H, m), 2.69–2.90 (2H, m), 3.39–3.54 (1H, m), 3.67 (3H, s), 3.74–3.85 (0.5H, m), 3.81 (6H, s), 3.98–4.12 (0.5H, m), 4.61 (0.5H, d, J=8.4 Hz), 4.76 (0.5H, d, J=8.6 Hz), 6.54 (0.5H, br s), 6.66 (1.5H, br s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 26.1, 26.2, 26.3, 27.0, 27.3, 29.7, 29.8, 30.6, 30.7, 39.0, 39.6, 52.3, 52.4, 55.7, 55.9, 56.0, 59.0, 59.7, 111.2, 111.4, 111.5, 111.6, 126.1, 126.4, 128.4, 128.9, 146.4, 146.5, 147.6, 147.7, 156.4, 156.7. FAB-LM *m/z*: 334 (M+H). FAB-HM Calcd for $C_{19}H_{28}NO_4$: 334.2018. Found: 334.2019.

4.3.7. *N*-(Methoxycarbonyl)-1-isopropyl-6,7-dimethyloxy-1,2,3,4-tetrahydroisoquinoline (2g). Colorless crystals. IR (neat) ν cm^{-1}: 1698, 1254. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.92–1.02 (6H, m), 1.92–2.19 (1H, m), 2.68–2.97 (2H, m), 3.30–3.54 (1H, m), 3.71 (3H, s), 3.74–3.92 (0.5H, m), 3.85 (6H, s), 4.06–4.17 (0.5H, m), 4.64 (0.5H, d, J=8.3 Hz), 4.78 (0.5H, d, J=8.5 Hz), 6.56–6.68 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 19.6, 19.7, 20.2, 20.3, 27.2, 27.4, 33.8, 33.9, 39.0, 39.6, 52.3, 52.5, 55.8, 55.9, 60.2, 60.3, 111.1, 111.2, 111.4, 111.5, 126.2, 126.4, 128.6, 129.1, 146.6, 146.7, 147.6, 147.7, 156.4, 156.7. FAB-LM *m/z*: 294 (M+H). FAB-HM Calcd for $C_{16}H_{23}NO_4$: 293.1627. Found: 293.1627.

4.3.8. *N*-(Methoxycarbonyl)-1-hexyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (4a). Colorless oil. IR (neat) ν cm^{-1}: 3329, 1672, 1232. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.78–0.98 (3H, m), 1.15–1.48 (8H, m), 1.58–1.89 (2H, m), 2.58–2.74 (1H, m), 2.75–2.92 (1H, m), 3.18–3.39 (1H, m), 3.74 (3H, s), 3.88–3.99 (0.5H, m), 4.07–4.17 (0.5H, m), 4.97 (0.5H, dd, J=9.2, 4.9 Hz), 5.07 (0.5H, dd, J=8.1, 5.7 Hz), 6.60 (1H, s), 6.67 (0.5H, d, J=8.4 Hz), 6.70 (0.5H, d, J=8.1 Hz), 6.89 (0.5H, d, J=8.1 Hz), 6.91 (0.5H, d, J=8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.6, 26.2, 28.2, 28.6, 29.0, 29.2, 31.8, 36.9, 37.1, 37.6, 38.1, 52.8, 54.6, 54.8, 113.6, 115.0, 115.2, 128.0, 128.2, 129.5, 129.7, 135.0, 135.2, 154.7, 156.6, 156.7. FAB-LM *m/z*: 292 (M+H). FAB-HM Calcd for $C_{17}H_{26}NO_3$: 292.1913. Found: 292.1896. Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found; C, 70.19; H, 8.56; N, 4.63.

4.3.8.1. *N*-(Methoxycarbonyl)-1-hexyl-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (*o*-4a). Colorless crystals. IR (KBr) ν cm^{-1}: 3324, 1670, 1126. ^1H NMR (300 MHz,

$CDCl_3$) δ: 0.78–0.97 (3H, m), 1.15–1.52 (8H, m), 1.53–1.72 (1H, m), 1.81–2.01 (1H, m), 2.74 (1H, ddd, J=16.4, 4.2, 3.4 Hz), 2.79–3.03 (1H, m), 3.21–3.45 (1H, m), 3.73 (1.5H, s), 3.76 (1.5H, s), 3.94–4.06 (0.5H, m), 4.15–4.27 (0.5H, m), 5.30 (0.5H, dd, J=10.3, 3.4 Hz), 5.46 (0.5H, dd, J=10.1, 3.8 Hz), 5.89 (1H, br s), 6.62 (1H, d, J=7.5 Hz), 6.64 (0.5H, br s), 6.67 (1H, d, J=7.5 Hz), 6.98 (0.5H, t, J=7.5 Hz), 7.00 (0.5H, t, J=7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.7, 26.2, 26.3, 27.9, 28.2, 29.0, 29.2, 31.8, 31.9, 33.5, 33.6, 36.9, 37.6, 50.5, 50.6, 52.6, 52.8, 112.8, 113.1, 120.4, 121.1, 125.6, 125.8, 126.9, 127.0, 134.9, 135.6, 151.9, 152.6, 156.7, 156.8. FAB-LM m/z: 292 (M+H). FAB-HM Calcd for $C_{17}H_{26}NO_3$: 292.1913. Found: 292.1908.

4.3.9. *N*-(Methoxycarbonyl)-1-phenyl-6-hydroxy-1,2,3,4-tetrahydroisoquinoline (4e). Colorless oil. IR (neat) ν cm^{-1}: 3318, 1672, 1232. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.65 (1H, dt, J=16.2, 3.9 Hz), 2.81–2.96 (1H, m), 3.16–3.32 (1H, m), 3.80 (3H, s), 3.88–4.15 (1H, m), 6.17–6.43 (1H, m), 6.64–6.76 (2H, m), 6.87 (1H, d, J=9.0 Hz), 7.11–7.31 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.4, 38.1, 53.0, 57.4, 113.8, 115.1, 126.8, 127.4, 128.2, 129.5, 136.2, 142.5, 155.1, 156.4. FAB-LM m/z: 284 (M+H). FAB-HM Calcd for $C_{17}H_{18}NO_3$: 284.1286. Found: 280.1275.

4.3.9.1. *N*-(Methoxycarbonyl)-1-phenyl-8-hydroxy-1,2,3,4-tetrahydroisoquinoline (*o*-4e). Colorless crystals. Mp 205–206 °C. IR (neat) ν cm^{-1}: 3334, 1660, 1247. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.71 (0.5H, dd, J=4.0, 3.6 Hz), 2.76 (0.5H, dd, J=3.8, 3.6 Hz), 2.87–3.07 (1H, m), 3.08–3.24 (1H, m), 3.74 (1.5H, s), 3.80 (1.5H, s), 3.86–4.13 (1H, m), 5.34 (0.5H, br s), 5.91 (0.5H, br s), 6.50 (0.5H, br s), 6.67 (1H, d, J=7.8 Hz), 6.72 (0.5H, br s), 6.76 (0.5H, d, J=7.8 Hz), 6.80 (0.5H, d, J=7.8 Hz), 7.12 (1H, t, J=7.8 Hz), 7.16–7.33 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.8, 28.2, 37.5, 37.8, 52.9, 53.2, 113.2, 113.5, 120.8, 121.3, 122.7, 127.5, 127.7, 128.0, 128.3, 136.2, 136.8, 141.1, 152.3, 152.8, 155.8, 156.4. FAB-LM m/z: 284 (M+H). FAB-HM Calcd for $C_{17}H_{18}NO_3$: 284.1286. Found: 284.1287.

4.3.10. *N*-(Methoxycarbonyl)-1-hexyl-6-methoxy-1,2,3,4-tetrahydroisoquinoline (6a). Colorless oil. IR (neat) ν cm^{-1}: 1701, 1230. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.73–0.88 (3H, m), 1.11–1.42 (8H, m), 1.49–1.78 (2H, m), 2.63 (1H, dt, J=16.3, 4.0 Hz), 2.72–2.96 (1H, m), 3.08–3.34 (1H, m), 3.65 (3H, s), 3.70 (3H, s), 3.81–3.94 (0.5H, m), 4.14–4.19 (0.5H, m), 4.92 (0.5H, dd, J=8.9, 4.4 Hz), 5.03 (0.5H, dd, J=7.9, 5.5 Hz), 6.56 (1H, s), 6.66 (0.5H, d, J=8.4 Hz), 6.67 (0.5H, d, J=8.4 Hz), 6.92 (0.5H, d, J=8.4 Hz), 6.95 (0.5H, d, J=8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.6, 26.0, 26.3, 28.5, 28.8, 29.1, 29.2, 31.8, 37.0, 37.1, 37.4, 38.1, 52.5, 54.3, 54.5, 55.2, 112.1, 112.4, 113.4, 127.9, 128.2, 130.3, 130.5, 135.1, 135.3, 156.3, 158.0. FAB-LM m/z: 306 (M+H). FAB-HM Calcd for $C_{18}H_{28}NO_3$: 306.2069. Found: 306.2070. Anal. Calcd for $C_{18}H_{27}NO_3$: C, 70.79; H, 8.91; N, 4.59. Found: C, 70.85; H, 8.97; N, 4.44.

4.3.10.1. *N*-(Methoxycarbonyl)-1-hexyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (*o*-6a). IR (neat) ν cm^{-1}: 1701, 1261. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87–0.93 (3H, m), 1.21–1.49 (8H, m), 1.53–1.96 (2H, m), 2.69 (0.4H, dd, J=4.5, 3.0 Hz), 2.74 (0.6H, dd, J=4.5, 3.1 Hz), 2.82–3.02 (1H, m), 3.19–3.41 (1H, m), 3.71 (3H, s), 3.81 (1.2H, s), 3.84 (1.8H, s), 3.98 (0.4H, ddd, J=13.4, 5.9, 3.1 Hz), 4.21 (0.6H, ddd, J=13.2, 6.3, 3.0 Hz), 5.26 (0.6H, dd, J=10.2, 3.3 Hz), 5.41 (0.4H, dd, J=9.9, 3.7 Hz), 6.66–6.75 (2H, m), 7.11 (0.4H, t, J=7.8 Hz), 7.13 (0.6H, d, J=7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.7, 26.1, 26.2, 27.8, 28.2, 28.9, 29.1, 31.8, 33.5, 33.6, 36.6, 37.4, 50.2, 50.3, 52.4, 52.5, 55.2, 107.7, 107.9, 120.9, 121.3, 126.9, 127.0, 127.2, 127.5, 134.9, 135.1, 155.5, 155.8, 156.3, 156.4. FAB-LM m/z: 306 (M+H). FAB-HM Calcd for $C_{18}H_{28}NO_3$: 306.2069. Found: 306.2066.

4.3.11. *N*-(Methoxycarbonyl)-1-phenyl-6-methoxy-1,2,-3,4-tetrahydroisoquinoline (6e). Colorless crystals. Mp 83–84 °C. IR (KBr) ν cm^{-1}: 1697, 1230. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.66 (1H, dt, J=16.1, 3.8 Hz), 2.81–3.01 (1H, m), 3.09–3.24 (1H, m), 3.70 (3H, s), 3.74 (3H, s), 3.82–4.19 (1H, m), 6.21 (0.5H, br s), 6.33 (0.5H, br s), 6.66 (1H, s), 6.68 (1H, d, J=8.2 Hz), 6.90 (1H, d, J=8.2 Hz), 7.05–7.28 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.7, 38.0, 52.7, 55.3, 57.3, 112.5, 113.4, 127.3, 127.5, 128.2, 129.5, 136.3, 142.8, 156.0, 158.4. FAB-LM m/z: 298 (M+H). FAB-HM Calcd for $C_{18}H_{20}NO_3$: 298.1491. Found: 298.1467. Anal. Calcd for $C_{18}H_{20}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.77; H, 6.51; N, 4.61.

4.3.11.1. *N*-(Methoxycarbonyl)-1-phenyl-8-methoxy-1,2,3,4-tetrahydroisoquinoline (*o*-6e). Pale yellow oil. IR (neat) ν cm^{-1}: 1697, 1230. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.67–2.80 (1H, m), 2.88–3.07 (1H, m), 3.09–3.29 (1H, m), 3.67 (1.5H, s), 3.68 (1.5H, s), 3.75 (1.5H, s), 3.81 (1.5H, s), 3.82–3.95 (0.5H, m), 3.94–4.10 (0.5H, m), 6.52 (0.5H, s), 6.68 (0.5H, s), 6.74 (1H, d, J=7.2 Hz), 6.81 (1H, t, J=7.2 Hz), 7.12 (1H, d, J=7.2 Hz), 7.16–7.32 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.8, 28.1, 37.7, 37.9, 52.8, 53.0, 55.4, 108.1, 120.8, 121.2, 126.9, 127.4, 127.7, 127.8, 128.0, 128.2, 136.1, 136.5, 141.9, 142.1, 156.0, 156.3. FAB-LM m/z: 298 (M+H). FAB-HM Calcd for $C_{18}H_{20}NO_3$: 298.1491. Found: 298.1485.

4.4. General procedure for PFOSA-catalyzed oxa-Pictet–Spengler reactions in HFIP–water

To a mixture of carbamate **9**, **11**, or **13** (0.42 mmol) and perfluorooctanesulfonic acid (PFOSA, 0.042 or 0.084 mmol) in HFIP–water (10 v/v %, 1.0 mL) was added aldehyde (0.50–2.0 mmol). After being stirred until the consumption of starting carbamate by TLC analysis, the reaction mixture was quenched with saturated aq $NaHCO_3$ and brine, and extracted with ether. The organic layer was dried over $MgSO_4$, and the filtrate was concentrated to dryness to give a crude mixture. Purification by silica gel column chromatography (hexane/AcOEt=10:1) gave a pure product **10** or **12**.

4.4.1. 6,7-Dimethoxy-1-hexyl-3,4-dihydro-1*H*-isochromene (10a). Colorless oil. IR (neat) ν cm^{-1}: 1514, 1107. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.86 (3H, t, J=6.8 Hz), 1.20–1.52 (8H, m), 1.70–1.89 (2H, m), 2.57 (1H, dt, J=16.0, 3.6 Hz), 2.82–2.92 (1H, m), 3.67–3.75 (1H, m), 3.83 (6H, s), 4.05–4.12 (1H, m), 4.65 (1H, dd, J=7.8, 2.7 Hz), 6.53 (1H, s), 6.56 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 13.9, 22.5, 25.1, 28.6, 29.3,

31.7, 36.0, 55.7, 55.9, 63.0, 75.4, 107.9, 111.4, 125.9, 130.4, 147.3. FAB-LM *m/z*: 279 (M+H). FAB-HM Calcd for $C_{17}H_{27}O_3$: 279.1961. Found: 279.1953.

4.4.2. 6,7-Dimethoxy-1-undecyl-3,4-dihydro-1*H*-isochromene (10b). Colorless crystals. Mp 41–43 °C. IR (KBr) ν cm^{-1}: 1522, 1111. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.80 (3H, t, *J*=6.7 Hz), 1.18–1.46 (18H, m), 1.62–1.79 (2H, m), 2.53 (1H, dt, *J*=15.9, 3.6 Hz), 2.78–2.88 (1H, m), 3.67–3.71 (1H, m), 3.78 (3H, s), 3.78 (3H, s), 4.01–4.07 (1H, m), 4.6 (1H, dd, *J*=8.0, 2.8 Hz), 6.48 (1H, s), 6.52 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.7, 25.3, 28.7, 29.4, 29.8, 29.9, 31.9, 36.1, 55.9, 56.0, 63.2, 75.6, 108.0, 111.5, 126.0, 130.5, 147.4. FAB-LM *m/z*: 349 (M+H). FAB-HM Calcd for $C_{22}H_{37}O_3$: 349.2742. Found: 349.2755. Anal. Calcd for $C_{22}H_{36}O_3$: C, 75.82; H, 10.41. Found: C, 75.52; H, 10.11.

4.4.3. 6,7-Dimethoxy-1-ethyl-3,4-dihydro-1*H*-isochromene (10c). Colorless oil. IR (neat) ν cm^{-1}: 1512, 1138. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.98 (3H, t, *J*=7.3 Hz), 1.70–1.85 (1H, m), 1.88–2.01 (1H, m), 2.59 (1H, dt, *J*=15.9, 3.6 Hz), 2.85–2.95 (1H, m), 3.70–3.78 (1H, m), 3.84 (3H, s), 3.85 (3H, s), 4.08–4.15 (1H, m), 4.58–4.65 (1H, m), 6.55 (1H, s), 6.59 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 9.50, 28.7, 28.8, 55.8, 56.0, 63.2, 107.9, 111.5, 126.2, 130.1, 147.4. FAB-LM *m/z*: 232.2 (M+H). FAB-HM Calcd for $C_{13}H_{19}O_3$: 223.1334. Found: 223.1335.

4.4.4. 6,7-Dimethoxy-3,4-dihydro-1*H*-isochromene (10d). Colorless crystals. Mp 60–62 °C. IR (KBr) ν cm^{-1}: 1516, 1095. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.70 (2H, t, *J*=5.7 Hz), 3.76 (3H, s), 3.78 (3H, s), 3.88 (2H, t, *J*=5.7 Hz), 4.63 (2H, s), 6.40 (1H, s), 6.54 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 27.8, 55.9, 65.4, 67.7, 107.3, 111.7, 125.0, 126.7, 147.5, 147.7. FAB-LM *m/z*: 195 (M+H). FAB-HM Calcd for $C_{11}H_{15}O_3$: 195.1021. Found: 195.1011. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found; C, 68.00; H, 7.36.

4.4.5. 6,7-Dimethoxy-1-phenyl-3,4-dihydro-1*H*-isochromene (10e). Colorless crystals. Mp 73–75 °C. IR (KBr) ν cm^{-1}: 1514, 1090. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.74 (1H, dt, *J*=16, 4.0 Hz), 2.99–3.09 (1H, m), 3.65 (3H, s), 3.85–3.93 (4H, m), 4.14 (1H, dt, *J*=11.3, 5.2 Hz), 5.68 (1H, s), 6.24 (1H, s), 6.66 (1H, s), 7.28–7.38 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 28.3, 55.9, 63.5, 79.1, 109.8, 111.2, 126.1, 128.1, 128.9, 128.9, 142.2, 147.3, 147.9. FAB-LM *m/z*: 271 (M+H). FAB-HM Calcd for $C_{17}H_{19}O_3$: 271.1334. Found: 271.1319. Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.21; H, 6.77.

4.4.6. 1-Cyclohexyl-6,7-dimethoxy-3,4-dihydro-1*H*-isochromene (10f). Colorless crystals. Mp 79–81 °C. IR (KBr) ν cm^{-1}: 1517, 1107. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.03–1.84 (11H, m), 2.47 (1H, d, *J*=15.8 Hz), 2.86–2.97 (1H, m), 3.65 (1H, ddd, *J*=11.1, 11.1, 3.0 Hz), 3.85 (3H, s), 3.85 (3H, s), 4.14 (1H, ddd, *J*=11.1, 5.8, 1.9 Hz), 4.56 (1H, s), 6.57 (1H, s), 6.58 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.6, 26.5, 26.5, 27.0, 29.0, 30.3, 43.8, 55.8, 56.1, 64.1, 79.8, 108.0, 111.4, 127.2, 129.3, 147.3, 147.3. FAB-LM *m/z*: 276 (M). FAB-HM Calcd for $C_{17}H_{25}O_3$: 277.1804. Found: 277.1831. Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.54; H, 8.60.

4.4.7. 6,7-Dimethoxy-1-isopropyl-3,4-dihydro-1*H*-isochromene (10g). Colorless crystals. Mp 48–50 °C. IR (KBr) ν cm^{-1}: 1512, 1103. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.71 (3H, d, *J*=6.8 Hz), 1.15 (3H, d, *J*=6.8 Hz), 2.19 (1H, qqd, *J*=6.8, 6.8, 2.7 Hz), 2.47 (1H, d, *J*=15.9 Hz), 2.89–2.99 (1H, m), 3.65 (1H, ddd, *J*=11.3, 11.3, 3.0 Hz), 3.84 (3H, s), 3.85 (3H, s), 4.16 (1H, ddd, *J*=11.3, 5.5, 1.7 Hz), 4.59 (1H, d, *J*=2.7 Hz), 6.56 (1H, s), 6.58 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 15.0, 19.8, 29.0, 33.4, 55.8, 56.0, 64.2, 79.9, 107.8, 111.4, 127.1, 129.8, 147.3, 147.5. FAB-LM *m/z*: 237 (M+H). FAB-HM Calcd for $C_{14}H_{21}O_3$: 237.1491. Found: 237.1483.

4.4.8. 1-Hexyl-6-methoxy-3,4-dihydro-1*H*-isochromene (12a). Colorless oil. IR (neat) ν cm^{-1}: 1502, 1105. ^1H NMR (300 MHz, $CDCl_3$) δ: 0.80 (3H, t, *J*=6.7 Hz), 1.18–1.46 (8H, m), 1.62–1.89 (2H, m), 2.59 (1H, dt, *J*=16.2, 3.6 Hz), 2.87 (1H, dd, *J*=9.4, 5.9 Hz), 3.63–3.68 (1H, m), 3.71 (3H, s), 4.01–4.08 (1H, m), 4.62 (1H, dd, *J*=8.1, 2.7 Hz), 6.56 (1H, d, *J*=2.7 Hz), 6.67 (1H, dd, *J*=8.5, 2.7 Hz), 6.92 (1H, d, *J*=8.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.1, 22.7, 25.2, 29.4, 29.5, 31.9, 36.1, 55.2, 63.1, 75.7, 112.4, 113.3, 125.9, 130.9, 135.2, 157.7. FAB-LM *m/z*: 249 (M+H). FAB-HM Calcd for $C_{16}H_{25}O_2$: 249.1855. Found: 249.1867.

4.4.9. 6-Methoxy-1-phenyl-3,4-dihydro-1*H*-isochromene (12e). The ^1H NMR spectra of **12e** were identical to that reported in the literature.[32]

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