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Design, Synthesis and Evaluation of Novel 2,6-Disubstituted Phenol Derivatives as General Anesthetics

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KEYWORDS anesthetics, $GABA_A$, 2,6-disubstituted phenol derivatives, water soluble prodrug, stereoselectivity

ABSTRACT A novel series of optically active 2,6-disubstituted alkylphenols with improved anesthetic profiles compared to widely used propofol were synthesized. The incorporation of the cyclopropyl group not only increased the steric effect but also introduced stereoselective effects over their anesthetic properties. Compounds **1**, **2** and **6** were selected as potential candidates for further pre-clinical development including studies of their water-soluble prodrugs. Clinical studies of candidate compound **6** (Haisco HSK3486) as a general anesthetic are performed in Australia and China.

INTRODUCTION

2,6-Disubstituted alkylphenols are well known for their anesthetic activities. Propofol (compound **33**), with a chemical name of 2,6-diisopropylphenol, working through γ-aminobutyric acid type A ($GABA_A$)-mediated inhibition of synaptic transmission, and the inhibition of glutamate release,[1,2] has gained wide acceptance as a central intravenous anesthetic in current clinical practice. It possesses favorable pharmacokinetic properties which allow rapid on-set and return of consciousness with little residual effects. [1,2] Compound **33** can be clinically used for induction and maintenance of general anesthesia, endoscopic procedural sedation and sedation of patients in intensive care.[1] Despite being an excellent anesthetic agent, compound **33** is associated with some limitations and disadvantages, such as injection pain, blood pressure decrease, respiratory depression caused apnea and ICU syndrome.[3-5] Thus, in clinical practice, sedation with compound **33** is restricted under certain circumstances. Many anesthetics undergoing clinical development are modified to overcome the shortcomings of compound **33**. However, an ideal drug that is entirely satisfactory has not been discovered.

Inspired by the improved sedative potency of a previously reported compound **33** analog (*R*, *R*)-2,6-di-sec-butylphenol (compound **34**) (PF0713),[6] we incorporated cyclopropyl group(s) into the 2, 6 side chains of compound **33** to decrease its lipophilicity, in the meantime breaking the symmetry of the compound **33** molecule by introducing one or more chiral centers. Therefore, we synthesized a series of 2,6-disubstituted phenol derivatives and evaluated the pharmacological features of these compounds in contrast to compound **33**. Several compounds were identified as potent general anesthetics that possess better properties than compound **33**.

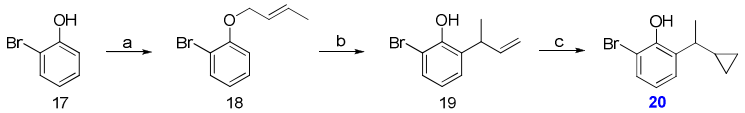
To circumvent problems associated with a lipid-based formulation of compound **33**[7], several water-soluble derivatives and prodrugs have been developed.[8,9] Efficacy and safety assessment of compound **35** (fospropofol) proved it to be the most suitable prodrug of compound **33** for

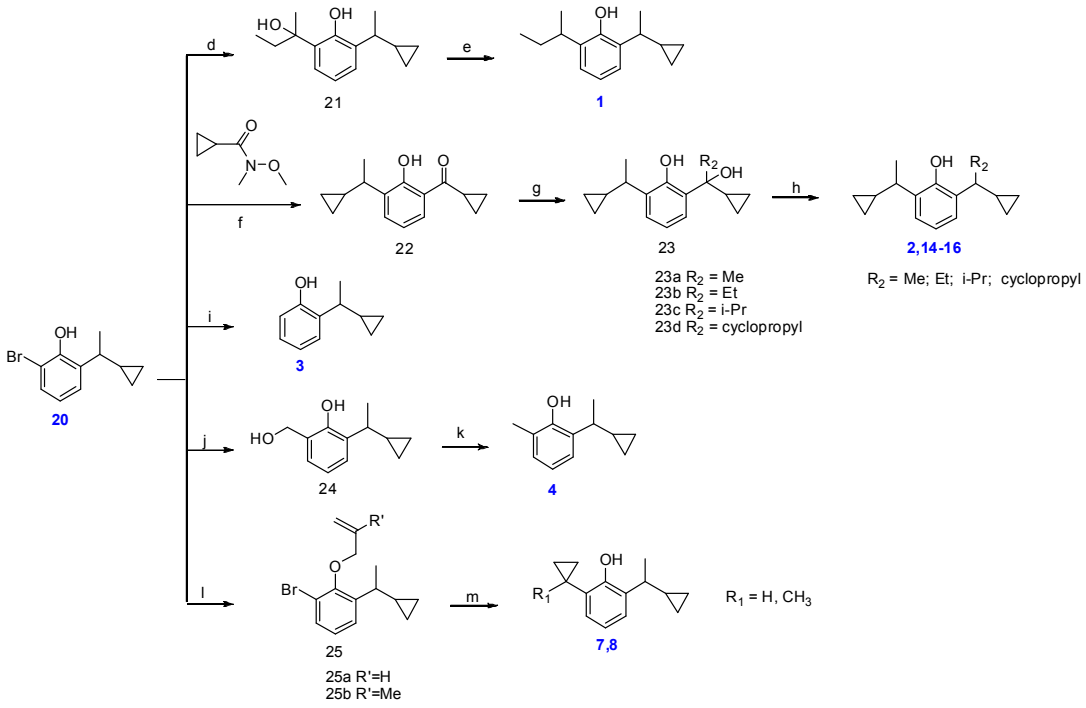
clinical development thus far.[10] However, compound **35** was reported to suffer from slow onset[11] and itching side effect[12]. This same modification was also evaluated for our selected compounds and proved to be able to overcome some of the existed drawbacks of compound **35**.

RESULTS AND DISCUSSION

Chemistry. A series of 2,6-disubstituted phenols were designed and prepared by the following methods (according to the following routes: **Schemes 1** and **2**). As shown in **Scheme 1**, most of the compounds were synthesized from the key intermediate **20**. 2-Bromophenol **17** reacted with 1-chlorobut-2-ene and NaOH to give compound **18**, which was subjected to thermal Claisen rearrangement in the presence of K_2CO_3 to produce compound **19**. Key intermediate **20** was synthesized via cyclopropanation. Intermediate **20** reacted with *n*-BuLi and 2-butanone to give alcohol **21** followed by dehydroxylation to produce compound **1**. Treatment of intermediate **20** with Weinreb amide in the presence of *n*-BuLi produced ketone **22**. Ketone **22** was treated with a Grignard reagent, which was followed by dehydroxylation in the presence of Et_3SiH and TFA to afford compounds **2** and **14-16**. Intermediate **20** was converted to compound **3** via *ortho*-lithiation and workup by protonic solvents. Hydroxymethylphenol **24** was obtained when intermediate **20** was treated with *n*-BuLi and paraformaldehyde. Dehydroxylation of compound **24** was carried out to give compound **4**. Alkylation of intermediate **20** produced compound **25** followed by Claisen rearrangement to give compounds **7** and **8**.

Scheme 1. Synthesis of derivatives of 2,6-disubstituted phenols from 2-bromophenol[a]

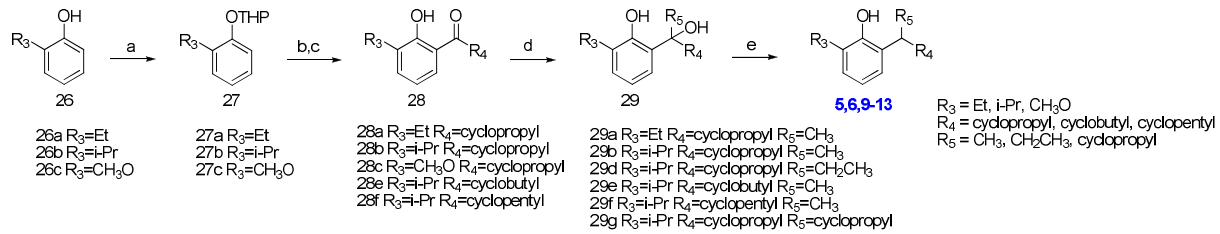




[a]Reagents and conditions:(a)1-chlorobut-2-ene, NaOH, DMF; (b) K_2CO_3, 200°C; (c) $AlEt_3$, CH_2I_2, DCM; (d) 2-butanone, *n*-BuLi, THF; (e) Et_3SiH, TFA, DCM; (f) Weinreb amide, *n*-BuLi, THF; (g) R_2MgBr, THF; (h) Et_3SiH, TFA, DCM; (i) *n*-BuLi, THF; (j) *n*-BuLi, $(HCHO)_n$, THF; (k) Et_3SiH, TFA, DCM; (l) allyl bromide, K_2CO_3, CH_3CN; (m) *n*-BuLi, TMEDA, Et_2O.

Other phenol analogs were synthesized by the approach outlined in **Scheme 2**. Substituted phenol **26** was treated with DHP in the presence of pyridinium 4-toluenesulfonate to afford protected phenol **27**, which reacted with *n*-BuLi and Weinreb amides, followed by hydrolysis to give compound **28**. Tertiary alcohol **29** was generated from the reaction of ketones **28** and Grignard reagents. Dehydroxylation of alcohol **29** was carried out in the presence of Et_3SiH and TFA to yield the desired series of compounds **5,** compound **6** (HSK3486)[13] and **9-13**.

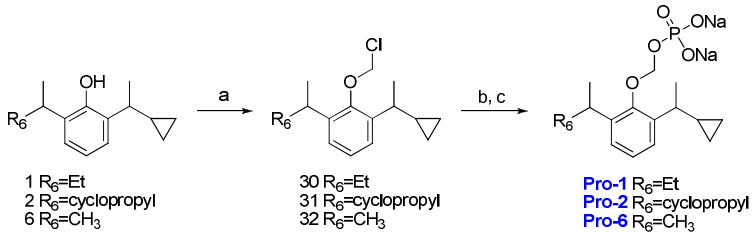
Scheme 2. Syntheses of derivatives of 2,6-disubstituted phenols from 2-substituted phenols [a]



[a]Reagents and conditions:(a) DHP, Pyridinium 4-toluenesulfonate, DCM; (b) Weinreb amides, *n*-BuLi, THF; (c) HCl, MeOH; (d) R_5MgBr,Toluene; (e) Et_3SiH, TFA, DCM.

Phosphono-*O*-methyl prodrugs of compounds **1**, **2** and **6** were prepared following the synthetic route depicted in **Scheme 3**. Compounds **1**, **2** or **6** reacted with bromochloromethane to form the corresponding phenol chloromethyl ethers. This intermediate was then treated with phosphorous acid, followed by treatment with NaOH to afford the target prodrug.

Scheme 3. Syntheses of Prodrugs of compound 1, 2 and 6[a]



[a]Reagents and conditions: (a) Bromochloromethane, NaOH, THF; (b) Phosphorous acid, TEA; (c) NaOH.

Biological Evaluation.

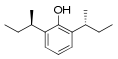
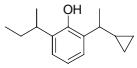
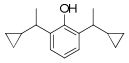
2,6-Disubstituted phenol derivatives as well as their pro-drugs have been extensively studied for their pharmacological actions especially in the anesthetic area.[14] As a generally accepted anesthesia, compound **33** is well known for its fast on-set and clean recovery from anesthesia, which is preferred by many anesthetists and clinicians. Compound **34**, a single diastereoisomer

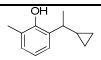
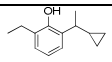
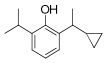
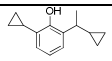
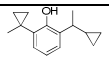
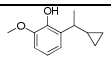
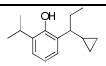
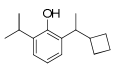
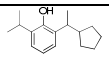
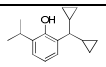
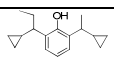
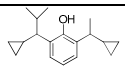
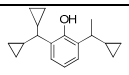
bearing two defined chiral centers of the *R*-configuration drew our attention.[6] Compound **34** not only resembles the structure of compound **33** but also displays a similar anesthetic potency. However, it shows a slower on-set and longer duration of anesthetic action. It is well known that individual enantiomers usually give significantly different pharmacological performance compared to their racemic mixtures.

A validated rodent model of general anesthesia[15,16] was used to provide a measure of on-set and duration of anesthesia as demonstrated by loss of righting reflex (LORR) experiments. These results allowed us to easily record and compare the on-set and recovery time of the compounds, which are the essential features of a general anesthetic for clinical usage. All compounds were prepared with 5% of dimethyl sulfoxide, 5-10% of Solutol HS-15 and 85-90% of saline, and administered to fasted ICR mice at a series of dosages (7-9 dosages per compound) by intravenous injection (n=10 per dose group), which required approximately 10 seconds per dose. Immediately following injection, the mice were placed on their backs continually until they stopped righting themselves. Anesthetic effect was assessed using on-set of LORR. And duration was monitored as the time it took until the mice regained the righting reflex while recovery time recorded as the time interval from return of righting reflex until the mouse was able to grip and climb a steel frame and ambulated normally, as assessed subjectively from behavioral observations. Therefore, the on-set, anesthetic duration and recovery time data were collected (**Table 1**) at doses could produce 100% lost of righting reflex of the mice. Most of the compounds (especially compounds with higher potency) possessed a fast on-set and quick recovery on mice, and they generally provided moderate to long anesthetic duration. It is well known that compound **33** may cause significant hypotension and respiratory depression.[3,4,17,18]

As compound **33** analogues, the designed molecules may also associate with side effects such as respiratory and cardiovascular depression which may be the cause of mortality in high doses.

Table 1. Evaluation studies on sedation profiles of compound 33, compound 34 and compounds 1-16[13]

Compound	Structure		On-set (sec)	Duration (sec)	Recovery time (sec)
33		-	<10	303.2±97.82	50.00±10.37
34		*R,R*	18.00±3.46	459.83±71.04	39.83±18.84
1		mix	<10	418.14±63.77	130.71±32.37
		R,R	<10	471.88±109.66	391.29±65.05
		R,S	<10	545.00±79.68	363.67±91.20
		S,R	<10	418.00±65.27	192.33±41.81
		S,S	<10	643.40±100.94	224.00±55.96
2		mix	<10	563.63±127.92	233.83±37.98
		R,R	<10	318.43±56.00	61.67±17.42
		R,S	<10	492.17±49.81	24.50±7.42
		S,S	7.00±1.41	567.33±69.46	150.80±37.51

3		mix	<10	598.00±165.64	329.60-43.83
4		mix	<10	198.33±53.50	122.00±58.17
5		mix	<10	409.57±33.86	226.57±81.01
6		mix	<10	518.50±48.47	78.00±37.60
		R	21.86±9.04	313.43±43.65	64.80±14.57
		S	5.71±1.38	344.00±68.96	168.33±71.71
7		mix	<10	500.67±46.89	193.63±144.59
8		mix	9.50±2.07	365.75±124.40	306.13±97.81
9		mix	<10	364.14±27.84	79.00±17.40
10		mix	13.60±8.26	523.57±23.16	50.38±42.52
11		mix	43.50±25.56	364.00±21.44	46.00±21.53
		R	<10	443.50±62.70	89.11±59.96
		S	15.63±2.67	450.43±50.32	191.80±4.38
12		mix	5.00±0.71	737.33±182.65	441.60±88.05
13		-	<10	2616.4±311.81	220.17±38.91
14		mix	7.50±1.05	670.13±185.18	205.8±65.30
15		mix	NA	NA	NA
16		mix	<10	761.33±189.10	326.50±73.22

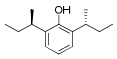
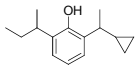
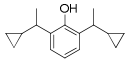
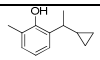
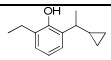
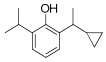
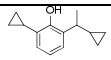
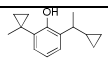
Using this LORR data, ED_{50} (50 % of the mice to lose righting reflex), LD_{50} (median lethal dose) and $HD_{10\ min}$ (the dose required to produce 10 min of anesthesia) were calculated by non-linear fitting using Graph Pad Prism5 to evaluate the relative efficacy of tested compounds. Compounds **1** and **2** and their diastereoisomers were synthesized and studied for their anesthetic properties (**Table 2**). They all show much lower ED_{50} which equates to a higher potency than compound **33**.

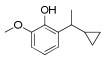
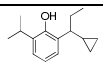
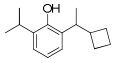
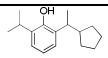
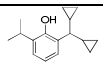
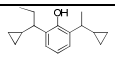
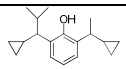
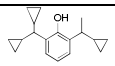
In order to further evaluate the effects of the steric bulk and potency, one side chain was modified while keeping one cyclopropyl ethyl side chain unchanged. Unsubstituted, methyl, ethyl, isopropyl, cyclopropyl and methoxy substituted cyclopropylethylphenol were evaluated accordingly. Sharing the same isopropyl group with compound **33**, compound **6** and its enantiomers presented the highest potency among this series of modified derivatives. The results from compounds **10** to **16** (**Table 2**) revealed that the increase of the steric bulk of the side chain may play a role in the decrease of potency.

10 min of anesthesia is a suitable time period for certain surgical operations or gastroscopy[19]. Therefore, $HD_{10\ min}$ is employed for the head to head evaluation between designed molecules and compound **33**. Among the evaluated diastereoisomers, (*R, R*)-configured diastereoisomers were found to have even higher potency than the other isomers.

Table 2. SAR study of compound 33, compound 34 and designed 2,6-disubstituted phenol derivatives (compounds 1-16)[13]

Entry	Structure		ED_{50} mg/Kg	LD_{50} mg/Kg	$HD_{10\ min}$ mg/Kg
33		-	11.70	31.3	25.0

34		*R,R*	2.69	23.8	10.0
1		mix	4.5	38.1	20.0
		R,R	2.0	14.3	7.5
		R,S	10.1	65.4	20.0
		S,R	1.3	8.3	4.0
		S,S	5.3	36.8	10.0
2		mix	3.6	>15.0	NA
		R,R	1.5	~6.3	5.0
		R,S	5.9	43.6	20.0
		S,S	19.5	149.0	40.0
3		mix	14.0	64.8	30.0
4		mix	7.4	54.9	NA
5		mix	7.7	57.1	NA
6		mix	3.7	22.7	10.0
		R	1.5	9.9	4.8
		S	7.9	50.0	30.0
7		mix	14.6	80.0	NA
8		mix	10.5	40.0	45.0

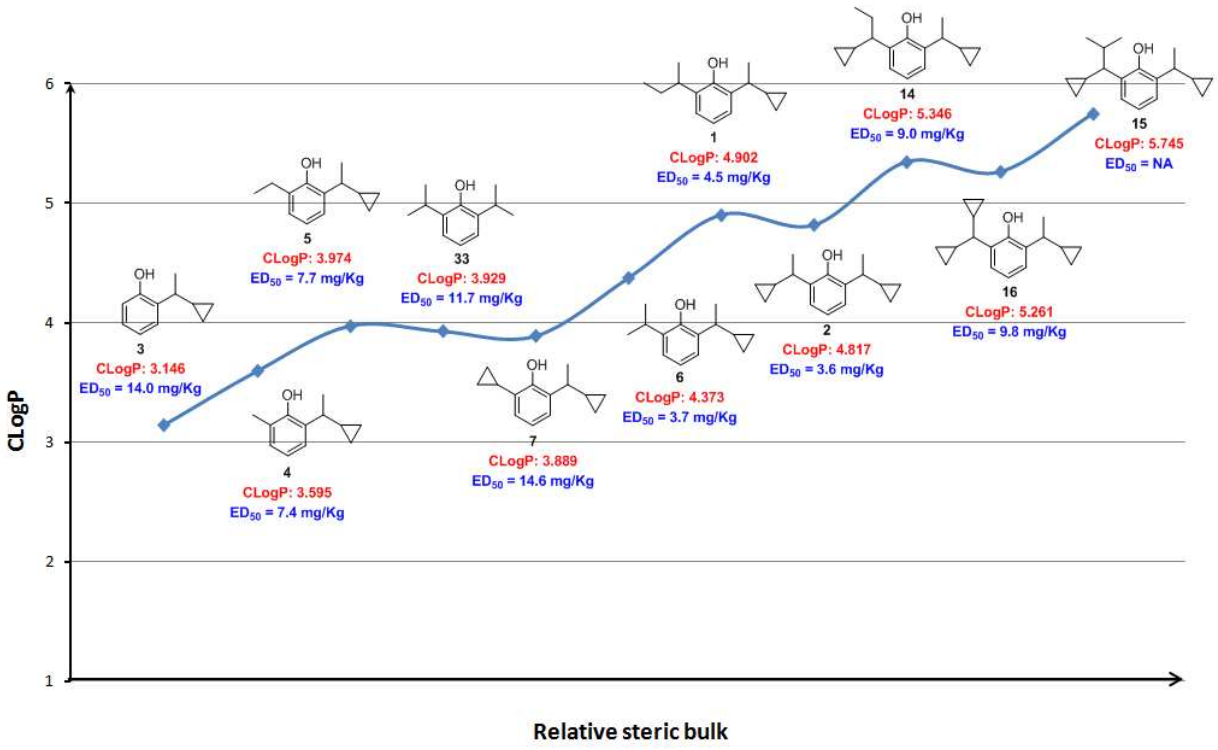
9		mix	7.4	67.0	NA
10		mix	6.2	53.2	NA
11		mix	7.1	40.0	NA
		R	6.6	38.2	NA
		S	46.1	107.0	100.0
12		mix	19.9	115.0	40.0
13		-	30.1	>100.0	50.0
14		mix	9.0	74.7	20.0
15		mix	NA	NA	NA
16		mix	9.8	98.2	20.0

Due to its aqueous insolubility, compound **33** was formulated as an oil-in-water emulsion.[20] The concentration of compound **33** in the aqueous phase is responsible for the pain upon injection, and previous research has demonstrated that the pain would be reduced when patients were injected with compound **33** with lower concentration in the aqueous phase of the emulsion[3]. The higher potencies of these modified compounds (**Table 2**) compared to compound **33** definitely give the potential to formulate at a lower concentration, which leads to less risk of injection pain.

In an attempt to make better sense of the influence of lipophilicity and steric bulk on the anesthetic effect of discussed phenol derivatives, we investigated their SAR by graphically relating their CLogP values with relative steric bulk. To better understand the general trend of steric hindrance, the 16 alkylphenols were divided into two groups, namely modification of both isopropyl side chains (**Figure 1-(a)**) and modification of one isopropyl side chain (**Figure 1-(b)**

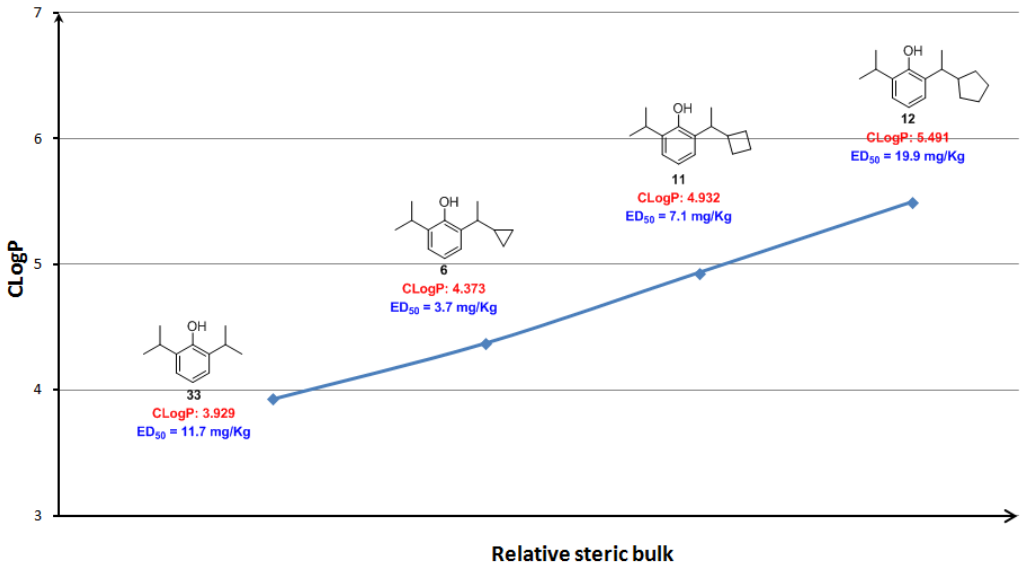
and **Figure 1-(c)**). The CLogP values showed a general increasing trend along with the increase of steric bulk. In general, compounds at the middle range of the graph possess both medium liphophilicity and suitable steric bulk resulting in better anesthetic potencies over compound **33**. **Figure 1-(a)** (compound **6**) shows that a minor structural change can produce a modest increase in CLogP with a dramatic effect on potency.

Figure 1-(a). General activity map according to steric bulk and CLogP of compound 33 and selected compounds.



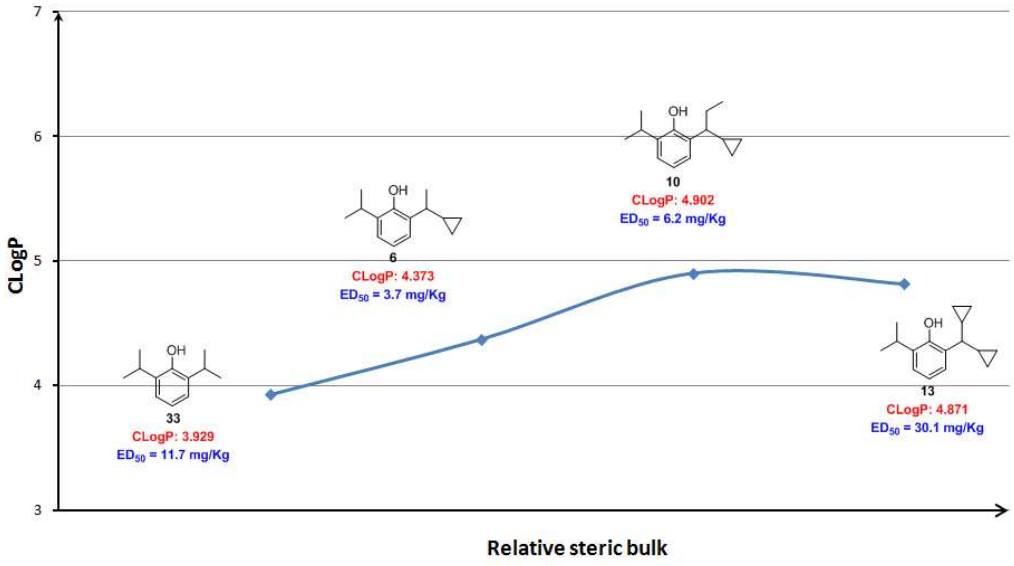
CLogP: data were calculated using Chemdraw/CLogP(Biobyte).

Figure 1-(b). General activity map according to steric bulk and CLogP of compound 33 and selected compounds.



CLogP: data were calculated using Chemdraw/CLogP(Biobyte).

Figure 1-(c). General activity map according to steric bulk and CLogP of compound 33 and selected compounds.

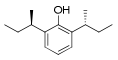
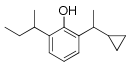
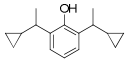
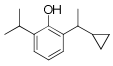


CLogP: data were calculated using Chemdraw/CLogP(Biobyte).

The systematic evaluation of the anesthetic properties of compounds **1**, **2** and **6** reveals their possible clinical usage as potential candidates to replace compound **33**. Molecular pharmacological studies have established that compound **33** is an allosteric potentiator and agonist of $GABA_A$ receptors.[21] To further evaluate the activity of above three compounds, a radioligand binding assay method was employed in this study. According to Maksay and Simonyi's study[22], crude synaptosomal membranes of cerebral cortex from male Wistar rats were used to test the selected compounds. Tested compounds with membrane suspensions in 20 mM Tris-HCl (pH 7.4) containing 200 mM NaCl were incubated with 2.0 nM [^{35}S]TBPS at 25°C for 3 hours. The resulted mixture was then filtered under vacuum and washed with 3 x 3 ml of ice-cold buffer. A scintillation counter was employed to measure the radioactivity of the filters. Nonspecific binding was determined in the presence of 200 μM picrotoxin. Concentration-dependent effects of tested compounds on [^{35}S]TBPS binding were expressed as % inhibition of control specific TBPS binding. The binding assay results (**Table 3**) are consistent with the *in vivo* LORR results. The *R*-configured enantiomers proved to have much higher potency than other isomers as well as compound **33**. This type of preference also demonstrated the stereoselectivity of $GABA_A$ receptor.

Table 3. $GABA_A$ receptor binding assay results of compound 33, compound 34 and compounds 1, 2 and 6.

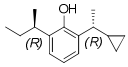
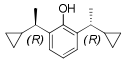
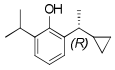
Entry	Structure		Binding assay (% inhibition)	
			(10μM)	(1μM)
33		-	~10 [23]	

34		*R,R*	29	0
1		mix	74	-3
		R,R	87	23
		R,S	34	-9
		S,R	63	-1
		S,S	47	5
2		mix	91	13
		R,R	96	64
		R,S	78	-5
		S,S	35	-11
6		mix	3	-12
		R	85	34
		S	-9	3

Selected *R*-configured diastereoisomers were administered to fasted rats at 1mg/kg intravenously (n=3 per group). The *i.v.* dose was formulated in 10% of dimethylacetamide, 20% Soltul HS-15 (30%，w/v) and 70% saline. Blood samples were collected into heparinized tubes predose and at 2, 4, 8, 12, 15 and 30 min, and at 1, 1.5 and 2 h via jugular vein after administration, then centrifuged at 5500 rpm for 10 min to obtain plasma samples. Plasma samples were stored at -40^{o}C until analysis. All compound concentrations were determined by liquid chromatography–tandem mass spectrometry (LC–MS/MS). Pharmacokinetic parameters were estimated by non-compartmental model using WinNonlin 6.3.

The pharmacokinetic profiles of selected analogues are shown in **Table 4**.

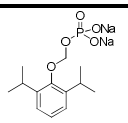
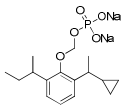
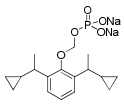
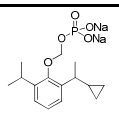
Table 4. Pharmacokinetic parameters of compound 33 and selected *R*-/*R,R*- configured optical isomers

Compounds	Structure	AUC(0-t) (ng.h/mL)	$T_{1/2}$ (min)	Vdss (L/kg)	CL (mL/kg.min)	C_{max} (mg/mL)
33		76.9	42	5.23	204	384
(*R,R*)-1		78.1	22	3.23	208	575
(*R,R*)-2		170.0	31	1.92	95	713
(*R*)-6		164.0	28	2.02	100	834

The same phosphono-*O*-methyl modification, as evidenced in compound **35**, was also introduced into our previously discussed compounds. Results from their evaluation studies on sedation profiles are shown in **Tables 5-7** which included experiments in mouse, rat, beagle dogs and minipigs.

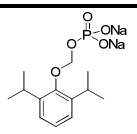
In the mouse model (**Table 5**), phosphate prodrugs of compounds **1**, **2** and **6** (referring as **Pro-1**, **Pro-2** and **Pro-6**) showed better efficacy than compound **35**. In accordance with previous results from their active compounds, prodrugs of *R*- and (*R,R*)- optical isomers displayed even higher TI up to twice the value of compound **35**. Studies in the rat model (**Table 6**) also proved that **Pro-6** and **Pro-2** had higher efficacy than compound **35** by four to six times.

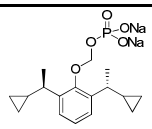
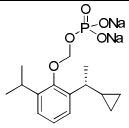
Table 5. Evaluation studies on anesthesia profiles of compound 35 and prodrugs of compounds 1, 2 and 6 in mouse

Compound	Structure		ED_{50} (mg/Kg)	LD_{50} (mg/Kg)	TI
35		-	94.97	220	2.3
Pro-1		*R,R*	15.89	63.68	4.0
		S,R	24.27	91.78	3.8
Pro-2		*R,R*	11.67	42.46	3.6
		R,S	35.79	142.8	4.0
		S,S	94.67	274.3	2.9
Pro-6		*R*	20.39	86.47	4.2
		S	82.66	369.8	4.5

$TI = LD_{50}/ED_{50}$

Table 6. Evaluation studies on anesthesia profiles of compound 35 and prodrugs of compounds 2 and 6 in rat

Compound	Structure		ED_{50} (mg/Kg)	LD_{50} (mg/Kg)	TI
35		-	40.98	189.0	4.61

Pro-2		*R,R*	7.34	40.44	5.51
Pro-6		*R*	12.94	61.36	4.74

Potent compounds **Pro-*(R,R)*-2** and **Pro-(*R*)-6** were selected for further evaluation in beagle dog and minipig model studies (**Table 7**). To perform a similar sedation effect, which includes similar sedation level and duration, **Pro-(*R,R*)-2** and **Pro-(*R*)-6** not only showed much shorter on-set and recovery time properties than compound **35**, but also required much lower dosages, down to one fifth of the amount required for compound **35**.

Table 7. Anesthetic effects following compounds 35, Pro-(*R,R*)-2 and Pro-(*R*)-6 bolus in beagle dogs or minipigs

Compound	Beagle dogs				Minipigs			
	Dosage (mg/Kg)	On-set min	Duration min	Recovery time min	Dosage (mg/Kg)	On-set min	Duration min	Recovery time min
35	75	2.1±0.2	80.4±4.4	7.3±4.5	22.5	1.6±0.6	72.6±15.6	6.0±2.5
Pro-(*R,R*)-2	12.5	0.9±0.1	70.2±10.7	3.3±2.7	4	3.0±0.7	65.8±13.1	9.6±4.5
Pro-(*R*)-6	25	0.7±0.1	72.2±10.6	11.2±6.8	5	1.6±0.1	68.2±13.8	4.8±1.1

CONCLUSION

In conclusion, we have developed a novel series of 2,6-disubstituted phenol analogs, which have proved to possess promising anesthetic properties. As potential candidates of general anesthetics, some of the analogs have much higher potency and tighter binding towards $GABA_A$ receptor while maintaining a fast on-set and recovery time compared to compound **33**. The sedation evaluation of water-soluble prodrugs of compounds **1**, **2** and **6** also demonstrated their better potency than compound **35** as well as their faster on-set and recovery time sedative profiles. Following the Phase I clinical studies in Australia and China, Phase II clinical trial with selected candidate, compound **6**, is now ongoing in China. And related clinical data will be reported in a separate paper.

EXPERIMENTAL SECTION

General procedures in Animal studies:

Sprague-Dawley rats (200-250g, male) and ICR mice (18-22g, male and female) involved in biology experiments were purchased from Vital River Co. LTD. Male and female beagle dogs and minipigs were purchased from Chengdu Dossy Experimental Animals Co., LTD. Animal facilities, animal care and study programs were conducted in conformity with in-house guidelines of Institute of Laboratory Animal Resources, Commission on Life Science, National Research Coulncil (National Academy Press, Washington, D.C., 2010). All animals were housed in cages at 21 ± 2^{o}C and provided free access to food and water. Rooms with constant temperature and humidity, were in a cycle of 12 h of light (8:00–20:00 h) and 12 h of dark (from 20:00 to 8:00 h).

Synthetic procedures in Chemistry:

All purchased reagents and starting materials were used without further purification. NMR spectra were recorded with a Bruker Avance 400 spectrometer (400 and 100 MHz for ^{1}H and ^{13}C NMR, respectively), with tetramethylsilane (TMS) as the internal standard; chemical shifts are expressed in parts per million (ppm, δ units). Mass spectra were acquired on FinniganLCQAd instrument (ESI). Most masses were reported as those of the protonated parent ions. Preparative column chromatography was performed using 200-300 mesh silica. All R_f values involved are from TLC. The title compounds were over 95% purity by HPLC.

2-(1-Cyclopropylethyl)-6-sec-butyl-phenol (1): To a solution of 2-bromo -6-(1-cyclopropylethyl)phenol **(20)** (10.00 g, 0.04 mol) in anhydrous THF (50.0 mL) was added dropwise *n*-BuLi (2.5 M in *n*-hexane, 50 mL, 0.12 mol) below 0°C under nitrogen atmosphere. Upon completion of the addition, the reaction mixture was stirred for 40 min at 0°C. *n*-Butanone (4.50 g, 0.06 mol) was added to the above mixture at -10°C. After removing the cooling bath, the mixture was stirred at room temperature overnight and then quenched with water (20 mL) and extracted with ethyl acetate (40 mL×3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography to give the crude dihydroxyl product **21** (6.80 g) as a yellow oil. R_f = 0.8 (petroleum ether/ethyl acetate = 50/1). This was used directly in the next step without further purification.

To a stirred solution of the crude dihydroxyl product **21** (6.80 g) and triethylsilane (6.00 g, 0.05 mol) in DCM (30 mL), TFA (11.70 g, 0.10 mol) was added dropwise below 0°C under a nitrogen atmosphere. Upon completion of the addition, the reaction mixture was stirred for 3 h at 0°C, quenched with ice-water (30 mL) and extracted with DCM (30 mL×2). To the combined organic

layers was added TBAF·$3H_2O$ (4.00 g，0.01 mol) and the mixture was stirred for 30 min at room temperature. The mixture was stirred with water (20 mL), extracted with DCM (20 mL×3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography to give 2-(1-cyclopropylethyl)-6-sec-butyl-phenol **(1)** (2.80 g, 32.06% yield over 2 steps, HPLC: 98.08%) as a pale yellow oil. R_f = 0.3 (petroleum ether/ethyl acetate = 50/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.18-7.14 (m, 1H), 7.09-7.06 (m, 1H), 6.97-6.12 (m, 1H), 4.95 (s, 1H), 2.99-2.94 (m, 1H), 2.61-2.54 (m, 1H), 1.77-1.61 (m, 2H), 1.38-1.35 (m, 3H), 1.32-1.29 (m, 3H), 1.14-1.09 (m, 1H), 0.98-0.93 (m, 3H), 0.65-0.59 (m, 1H), 0.54-0.48 (m, 1H), 0.30-0.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.70, 132.84, 132.81, 132.00, 131.89, 124.90, 124.36, 120.49, 37.31, 37.19, 34.20, 34.14, 30.18, 30.07, 20.51, 20.09, 20.06, 17.01, 12.27, 4.37, 4.33, 3.82, 3.68. HRMS (ESI) Calcd. for $C_{15}H_{22}O$ $[M+H]^+$: 219.17042. Found: 219.17425. Anal. Calcd. for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 81.49; H, 10.31.

2-[(1*S*)-1-Cyclopropylethyl]-6-sec-butyl-phenol [(*S*)-1] and **2-[(1*R*)-1-cyclopropylethyl]-6-sec-butyl-phenol [(*R*)-1]** were prepared from 2-bromo-6-[(1*R*)-1-cyclo-propylethyl]phenol [**(*S*)-20**] and 2-bromo-6-[(1*R*)-1-cyclo-propylethyl]phenol [**(*R*)-20**], referring to racemic mixture 1. The HRMS spectra of **(*R*)-1** and **(*S*)-1** are the same as **1**. **(*S*)-1** and **(*R*)-1**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12-7.09 (m, 1H), 7.01 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 4.88 (s, 1H), 2.93-2.87 (m, 1H), 2.56-2.46 (m, 1H), 1.69-1.55 (m, 2H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.24 (d, *J* = 6.8 Hz, 3H), 1.08-1.02 (m, 1H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.58-0.53 (m, 1H), 0.49-0.43 (m, 1H), 0.23-0.16 (m, 2H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.63, 132.77, 132.75, 131.94, 131.83,

124.85, 124.83, 124.31, 120.41, 37.25, 37.14, 34.14, 34.08, 30.11, 30.00, 20.45, 20.03, 20.00, 16.95, 16.93, 12.22, 4.30, 4.27, 3.77, 3.63.

2-[(1*S*)-1-Cyclopropylethyl]-6-[(1*R*)-1-methylpropyl]phenol [(*S*,*R*)-1] and **2-[(1*S*)-1-cyclopropylethyl]-6-[(1*S*)-1-methylpropyl]phenol [(*S*,*S*)-1]**: 2-(1-Cyclopropylethyl)-6-sec-butyl-phenol **(1)** (0.50 g) was separated by chiral HPLC to afford two optical isomers. Preparative condition: (instrument: Agilent 1260/ LH-Y-J0371(4-1); Column: CHIRALCEL OJHS (0.46 cm I.D. × 15 cm L); Mobile phase: *i*-PrOH/hexane=1/100; flow rate: 1.0 mL/min; backpressure: 100 bar; temperature: 35^{o}C; Wave length: 214 nm; time: 10 min).

Peak 1 **[(*S*,*R*)-1]**: 0.19 g, HPLC: 95.90%, pale yellow oil, chiral HPLC retention time = 3.61 min. HRMS m/z (ESI) is the same as **1**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.01 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 4.88 (s, 1H), 2.93-2.87 (m, 1H), 2.56-2.49 (m, 1H), 1.69-1.55 (m, 2H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.24 (d, *J* = 6.8 Hz, 3H), 1.08-1.02 (m, 1H), 0.89 (t, *J* = 7.2 Hz, 3H), 0.58-0.53 (m, 1H), 0.49-0.43 (m, 1H), 0.24-0.13 (m, 2H) . ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.63, 132.77, 131.84, 124.83, 124.28, 120.41, 37.12, 34.06, 30.11, 20.44, 20.00, 16.92, 12.20, 4.26, 3.61.

Peak 2 **[(*S*,*S*)-1]**: 0.20 g, HPLC: 98.66%, pale yellow oil, chiral HPLC retention time = 4.21 min. HRMS m/z (ESI) is the same as **1**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.11 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.02 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 2.94-2.86 (m, 1H), 2.54-2.46 (m, 1H), 1.71-1.55 (m, 2H), 1.30 (d, *J* = 7.0 Hz, 3H), 1.25 (d, *J* = 6.9 Hz, 3H), 1.09-1.01 (m, 1H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.60-0.53 (m, 1H), 0.45-0.43 (m, 1H), 0.24-0.13 (m, 2H). ^{13}C NMR

(100 MHz, $CDCl_3$): δ 150.62, 132.75, 131.94, 124.83, 124.30, 120.41, 37.25, 34.14, 29.99, 20.45, 20.03, 16.95, 12.21, 4.30, 3.76.

2-[(1*R*)-1-Cyclopropylethyl]-6-[(1*S*)-1-methylpropyl]phenol [(*R*,*S*)-1] and 2-[(1*R*)-1-cyclo propylethyl]-6-[(1*R*)-1-methylpropyl]phenol [(*R*,*R*)-1] : 2-[(1*R*)-1-Cyclopropylethyl]-6-sec-butyl-phenol (1.00 g) was separated by chiral HPLC to afford two optical isomers. **Preparative condition: (**Instrument: GX-281/CH-Y-C0630; Column: CHIRALPAK OJ-H (4.6 mm×150 mmL, 5μm); Mobile phase: *i*-PrOH/hexane=0/100; flow rate: 1.0 mL/min; backpressure: 100 bar; temperature: 35^{o}C; Wave length: 210 nm; time: 8 min).

Peak 1 **[(*R*,*R*)-1]:** 0.35 g, HPLC: 97.75%, pale yellow oil, chiral HPLC retention time = 4.98 min. ^{1}H NMR, ^{13}C NMR and HRMS spectra are the same as its enantiomer **[(*S*,*S*)-1]**.

Peak 2 **[(*R*,*S*)-1]:** 0.32 g, HPLC: 95.77%, pale yellow oil, chiral HPLC retention time = 5.28 min. ^{1}H NMR, ^{13}C NMR and HRMS spectra are the same as its enantiomer **[(*S*,*R*)-1]**.

2,6-Bis(1-cyclopropylethyl)phenol (2) : To a stirred solution of 2-(1-cyclopropylethyl)-6-(1-cyclopropyl-1-hydroxy-ethyl)phenol **(23a)** (3.20 g, 12.99 mmol) and triethylsilane (4.53 g, 38.97 mmol) in 30 mL dichloromethane was added dropwise TFA (11.85 g, 103.92 mmol) below 0^{o}C under a nitrogen atmosphere. Upon completion of the addition, the reaction mixture was stirred for 3h at 0^{o}C. The reaction solution was quenched with 100 mL ice-water and extracted with dichloromethane (50 mL×2). To the combined organic layers was added TBAF·3H_2O (12.27 g，38.97 mmol) and the mixture stirred for 30 min at ambient temperature. The mixture

was added to 500 mL water and extracted with dichloromethane (50 mL×3). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography to give the title compound **2** (2.75 g, 91.91% yield, HPLC: 95.56%) as a pale yellow oil. R_f = 0.6 (petroleum ether/ethyl acetate = 50/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 5.07 (s, 1H), 2.55-2.47 (m, 2H), 1.31 (d, *J* = 7.2 Hz, 6H), 1.10-1.02 (m, 2H), 0.61-0.43 (m, 4H), 0.26-0.14 (m, 4H). HRMS (ESI): Calcd. for $C_{16}H_{22}O$ $[M+H]^+$: 231.17042. Found: 231.17425. Anal. Calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.63. Found: C, 83.45; H, 9.60.

2,6-Bis[(1*R*)-1-cyclopropylethyl]phenol (*R,R*)-2, **2-[(1*R*)-1-cyclopropylethyl]-6-[(1*S*)-1-cyclopropylethyl]phenol (*R,S*)-2** and **2,6-bis[(1S)-1-cyclopropylethyl]phenol (*S,S*)-2**: The compound 2,6-bis(1-cyclopropylethyl)phenol **(2)** (4.80 g，20.84 mmol) was separated on Chiral Column (CHIRALPAK OZ-H, hexane/isopropanol(v/v) = 100/0, 1.0 mL/min, UV = 214 nm，temperature：35°C) to obtain the compound **(*R,R*)-2** (0.71 g, 59.17% yield, HPLC: 98.48%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 7.6 Hz, 2H), 6.89 (t, *J* = 7.6 Hz, 1H), 5.05 (s, 1H), 2.54-2.46 (m, 2H), 1.30 (d, *J* = 6.8 Hz, 6H), 1.09-1.03 (m, 2H), 0.60-0.54 (m,2H), 0.49-0.43 (m, 2H), 0.25-0.14 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.76, 132.13, 125.15, 120.37, 37.12, 20.07, 16.98, 4.35, 3.79. Compound **(*R,S*)-2** (1.30 g, 54.16% yield, HPLC: 97.23%) was obtained as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (d, *J* = 7.6 Hz, 2H), 6.91 (t, *J* = 7.6 Hz, 1H), 5.07 (s, 1H), 2.56-2.48 (m, 2H), 1.31 (d, *J* = 6.8 Hz, 6H), 1.09-1.02 (m, 2H), 0.60-0.54 (m, 2H), 0.50-0.43 (m, 2H), 0.26-0.15 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.77, 132.11, 125.15, 120.36, 37.16, 20.04, 17.03, 4.33, 3.76. Compound **(*S,S*)-2** (0.72 g, yield 60.0%, HPLC: 98.25%) was obtained as a white solid. ^{1}H NMR (400 MHz,

$CDCl_3$): δ 7.14 (d, *J* = 7.6 Hz, 2H), 6.90 (t, *J* = 7.6 Hz, 1H), 5.05 (s, 1H), 2.54-2.47 (m, 2H), 1.30 (d, *J* = 6.8 Hz, 6H), 1.09-1.02 (m, 2H), 0.60-0.54 (m, 2H), 0.49- 0.42 (m, 2H), 0.25-0.14 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.75, 132.12, 125.15, 120.36, 37.21, 20.06, 16.97, 4.34, 3.78.

2-(1-Cyclopropylethyl)phenol (3): To a solution of 2-bromo-6-(1-cyclopropylethyl)phenol **(20)** (1.40g, 5.8 mmol) in 10 mL anhydrous THF was added dropwise *n*-BuLi solution (2.5M in *n*-hexane, 20 mL, 50 mmol) below 0^{o}C under a nitrogen atmosphere. Upon completion of the addition, the reaction mixture was stirred for 3h at 0^{o}C. The mixture was quenched with 10 mL saturated aqueous NH_4Cl and extracted with ethyl acetate (20 mL×3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography to give the title product **3** (0.80 g, HPLC: 97.36%, 80% yield) as a pale yellow oil. R_f = 0.5 (petroleum ether/ ethyl acetate = 10/1). ^{1}H NMR: (400 MHz，$CDCl_3$): δ 7.30 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.11-7.07 (m, 1H), 6.95-9.91 (m, 1H), 6.75 (dd, *J* = 1.2, 8.0 Hz, 1H), 4.79 (s, 1H), 2.50-2.43 (m, 1H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.11-1.03 (m, 1H), 0.62-0.55 (m, 1H), 0.48-0.42 (m, 1H), 0.28-0.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.93, 133.98, 127.77, 126.80, 120.86, 115.35, 37.43, 20.16, 17.06, 4.49, 3.79. HRMS (ESI) Calcd. for $C_{11}H_{14}O$ $[M+H]^+$: 163.10782. Found: 163.11173. Anal. Calcd. for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 80.74; H, 8.82.

2-(1-Cyclopropylethyl)-6-methyl-phenol (4): 2-(1-Cyclopropylethyl)-6-(hydroxymethyl)-phenol **(24)** (1.50 g, 7.80 mmol) was dissolved in 8 mL of DCM. Triethylsilane (1.93 g, 16.73

mmol) and TFA (2.40 mL, 33.45 mmol) were added to the previous solution at -15°C. The reaction was kept at room temperature overnight before being quenched with ice water. The aqueous phase was extracted with DCM (10 mL×2). The combined organic layers were washed with saturated sodium bicarbonate solution (20 mL×2). To the organic phase was added TBAF·3H_2O (1.23 g，3.90 mmol), the mixture stirred for 1 h, washed with water (30 mL × 3), brine (30 mL), dried with anhydrous sodium sulfate and concentrated. The residue was purified by chromatography on silica gel to afford 2-(1-cyclopropylethyl)-6-methyl-phenol **(4)** as a colorless oil (0.51 g，37% yield, HPLC: 95.41%). R_f = 0.3 (petroleum ether/ethyl acetate = 40/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.02-7.00 (m, 1H), 6.86 (t, *J* = 7.6 Hz, 1H), 4.77 (s, 1H), 2.52-2.45 (m, 1H), 2.28 (s, 3H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.09-1.05 (m, 1H), 0.60-0.55 (m, 1H), 0.48-0.44 (m, 1H), 0.29-0.24 (m, 1H), 0.23-0.16 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 151.39, 132.16, 128.35, 125.48, 123.02, 120.35, 37.52, 20.14, 17.07, 16.01, 4.45, 3.88. HRMS (ESI): Calcd. for $C_{14}H_{18}O$ $[M+H]^+$: 177.12347. Found: 177.12735.

2-(1-Cyclopropylethyl)-6-ethyl-phenol (5)： 2-(1-Cyclopropyl-1-hydroxy-ethyl)-6-ethyl-phenol **(29a)** (1.00 g, 4.85 mmol) was dissolved in 8 mL of DCM at -15°C. Triethylsilane (1.20 g, 10.4 mmol) and TFA (1.5 mL, 20.80 mmol) were added to the reaction solution which was stirred at -10°C for 1 hr. The reaction was kept at room temperature overnight before being quenched with ice water. The aqueous phase was extracted with DCM (10 mL×2) and washed with saturated sodium bicarbonate solution (20 mL×2). To the organic phase was added TBAF·3H_2O (0.75 g, 2.43 mmol), the mixture stirred for 1 hr, washed with water (30 mL × 3), brine (30 mL), dried with anhydrous sodium sulfate, then concentrated and purified by flash chromatography on silica gel to afford the desired product **5** as a colorless oil (0.68 g, 70% yield, HPLC: 96.27%). R_f = 0.3 (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.16 (dd, *J* = 1.6, 7.6

Hz, 1H), 7.03 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 4.85 (s, 1H), 2.65 (q, *J* = 7.6 Hz, 2H), 2.54-2.47 (m, 1H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.28 (t, *J* = 7.6 Hz, 3H), 1.11-1.03 (m, 1H), 0.60-0.55 (m, 1H), 0.47-0.44 (m, 1H), 0.28-0.22 (m, 1H), 0.21-0.16 (m, 1H). HRMS (ESI): Calcd. for $C_{13}H_{18}O$ $[M+H]^+$: 191.13912. Found: 191.14304.

2-(1-Cyclopropylethyl)-6-isopropylphenol (6): To a stirred solution of 2-(1-cycloprop l-1-hydroxy-ethyl)-6-sopropyl-phenol **(29b)** (3.00 g, 13.62 mmol) and triethylsilane (6.40 g, 55.04 mmol) in DCM (25 mL) was added TFA (12.60 g, 110.51 mmol) dropwise at 0°C. Upon completion of the addition, the reaction mixture was stirred at 0°C for 2 hrs. The mixture was washed sequentially with water (50 mL) and saturated $NaHCO_3$ (50 mL). To the organic phase was added TBAF·$3H_2O$ (2.20 g, 6.97 mmol), the mixture stirred for 1 h, washed with water (30 mL × 3), brine (30 mL), dried over anhydrous sodium sulfate, evaporated, and purified by column chromatography to afford 2-(1-cyclopropylethyl)-6-isopropylphenol **(6)** as a colorless oil (2.0 g, 71.6% yield, HPLC: 98.42%). R_f = 0.5 (petroleum ether/ethyl acetate = 100/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.08 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 4.93 (s, 1H), 3.16 (hept, *J* = 6.9 Hz, 1H), 2.50 (m, 1H), 1.29 (d, *J* = 7.0 Hz, 3H), 1.26 (d, *J* = 6.9 Hz, 6H), 1.07-1.05 (m, 1H), 0.58-0.45 (m, 2H), 0.24-0.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.37, 133.83, 131.94, 124.99, 123.65, 120.49, 37.27, 27.13, 22.73, 20.04, 16.97, 4.33, 3.81. HRMS (ESI): Calcd. for $C_{14}H_{20}O$ $[M+H]^+$: 205.15477. Found: 205.15865. Anal. Calcd. for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 81.86; H, 9.91.

(*S*)-2-(1-cyclopropylethyl)-6-isopropylphenol [(*S*)-6] or ***(R)*-2-(1-cyclopropyl ethyl)-6-isopropylphenol [(*R*)-6]**: 2-(1-cyclopropylethyl)-6-isopropylphenol (6) (0.50 g) was separated by chiral HPLC to afford two optical isomers.

Preparative condition: (instrument: Agilent 1260/ LH-Y-J0371(4-1); Column: Chiralpak OJ-H (4.6 mm × 25 cm, 5 micron particles); Mobile phase: *n*-hexane; flow rate: 1.0 mL /min; backpressure: 100 bar; temperature: 35^{o}C; Wave length: 275 nm; time: 30 min)

Peak 1 **[(*R*)-6]**: 0.21 g, HPLC: 98.43%, pale yellow oil, chiral HPLC retention time = 11.48 min. ^{1}H NMR, ^{13}C NMR and HRMS spectra are the same as **6**.

Peak 2 **[(*S*)-6]**: 0.20 g, HPLC: 97.28%, pale yellow oil, chiral HPLC retention time = 14.46 min. ^{1}H NMR, ^{13}C NMR and HRMS spectra are the same as **6**.

2-Cyclopropyl-6-(1-cyclopropylethyl)phenol (7)： 2-(Allyloxy)-1-bromo-3-(1-cyclopropyl-ethyl)benzene **(25a)** (10.00 g, 35.81 mmol) and anhydrous diethyl ether (200 mL) were added to the flask under nitrogen protection. The mixture was cooled to -75 ^{o}C. *n*-Butyllithium (30 mL, 2.5 M) was then added, following by 1hr of stirring before the addition of *N*,*N*,*N*,*N*-tetramethylethylenediamine (9.57 g， 82.37 mmol). The system was warmed up to room temperature and stirred for another 10 hrs before saturated ammonium chloride (100 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (200 mL×2). The combined organic phases were washed with saturated NaCl (200 mL×2) solution, dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford 2-cyclopropyl-6-(1-

cyclopropylethyl)phenol **(7)** as a yellow oil (0.48 g, 6.6 % total yield, HPLC: 99.73%). R_f = 0.2 (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.99 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 5.60 (s, 1H), 2.53-2.45 (m, 1H), 1.77-1.74 (m, 1H), 1.33 (d, *J* = 7.2 Hz, 1H), 1.14-1.03 (m, 1H), 1.01-0.96 (m, 2H), 0.69-0.65 (m, 2H), 0.58-0.54 (m, 1H), 0.44-0.38 (m, 1H), 0.27-0.16 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.92, 132.67, 126.65, 126.55, 125.98, 119.85, 37.71, 20.43, 17.27, 9.56, 5.14, 4.64, 3.92. HRMS (ESI): Calcd. for $C_{14}H_{18}O$ $[M+H]^+$: 203.13912. Found: 203.14307.

2-(1-Cyclopropylethyl)-6-(1-methylcyclopropyl)phenol (8): 1-Bromo-3-(1-cyclopropyl-ethyl)-2-((2-methylallyl)oxy)benzene **(25b)** (10.57 g，35.81 mmol) and anhydrous ether (200 mL) was added to the flask. The mixture was cooled to -75^{o}C followed by the slow addition of *n*-butyllithium (30 mL, 2.5 M). The reaction mixture was stirred below -75^{o}C for 1 hr. before the addition of *N*,*N*,*N*,*N*- tetramethylethylenediamine (9.57 g，82.37 mmol). Then the system was warmed up to room temperature and stirred for another 10 hrs before saturated ammonium chloride (100 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate (200 mL×2), the combined organic phases were washed with saturated NaCl (200 mL×2), dried with anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford 2-(1-cyclopropylethyl)-6- (1-methylcyclopropyl)phenol **(8)** as a yellow oil (0.60 g, 8.01 % total yield, HPLC: 99.22%). R_f = 0.2 (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.09 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 5.75 (s, 1H), 2.54-2.46 (m, 1H), 1.34 (s, 3H), 1.31 (d, *J* = 7.2 Hz, 3H), 1.09-1.00 (m, 1H), 0.84-0.79 (m, 4H), 0.58-0.52 (m, 1H),0.42-0.36 (m,

1H), 0.23-0.18 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.10, 133.21, 130.10, 127.27, 126.01, 119.96, 37.55, 25.37, 17.33, 16.90, 13.04, 13.03, 4.65, 3.87. HRMS (ESI): Calcd. for $C_{15}H_{20}O$ $[M+H]^+$: 217.15477. Found: 217.15863.

2-(1-Cyclopropylethyl)-6-methoxy-phenol (9): To a stirred solution of 2-(2-methoxyphenoxy)tetrahydropyran **(27c)** (20.00 g, 96.04 mmol) in anhydrous THF (30 mL) was added *n*-BuLi (46.00 mL, 2.5 M in hexane, 115.00 mmol) dropwise under nitrogen atmosphere at -20°C. Upon completion of the addition, the reaction mixture was stirred at room temperature for 1 h, followed by the addition of *N*-methoxy-*N*-methylcyclopropanecarboxamide (18.60 g，144.01 mmol) at -20°C. Upon completion of the addition, the reaction mixture was stirred at room temperature for another 2 hrs, quenched with saturated ammonium chloride (20 mL), and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine (20 mL), dried over anhydrous sodium sulfate, and evaporated to give cyclopropyl-(3-methoxy-2-tetrahydropyranyloxyphenyl) methanone as a brown oil (28.00 g, crude). To the resulting oil in MeOH (56 mL) was added HCl (56 mL, 2 M, 112.00 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 0.5 h, quenched with saturated sodium hydrogen carbonate solution to pH=6, evaporated to remove MeOH, and extracted with Et_2O (50 mL × 3). The combined organic layers was washed with brine (50 mL), dried over anhydrous sodium sulfate, evaporated to afford cyclopropyl-(2-hydroxy-3-methoxyphenyl)methanone as a brown oil (19.00 g, crude). To a stirred solution of the resulting oil (19.00 g, crude) in anhydrous THF (100 mL) was added MeMgBr (82.30 mL, 3.0 M in Et_2O, 246.90 mmol) dropwise under an argon atmosphere at -30°C. Upon completion of the addition, the reaction mixture was stirred at room temperature for 2 hrs, quenched with saturated ammonium chloride (100 mL), and extracted with EA (100 mL × 3). The combined organic layers were washed with brine (100 mL), dried over

anhydrous sodium sulfate and evaporated to afford 2-(1-cyclopropyl-1-hydroxy-ethyl)-6-methoxy-phenol **(28c)** as a light yellow oil (6.50 g, crude). To a stirred solution of the residue (6.40 g, crude) and triethylsilane (7.20 g, 61.92 mmol) in DCM (30 mL) was added TFA (28.0 g, 245.57 mmol) dropwise while maintaining the temperature at 0°C. Upon completion of the addition, the reaction mixture was stirred at 0 °C for 2 hrs, washed with water (50 mL) and saturated $NaHCO_3$ (50 mL). To the organic phase was added TBAF·$3H_2O$ (4.90 g， 15.53 mmol), the mixture stirred for 1 h, washed with water (30 mL × 3), brine (30 mL), dried over anhydrous sodium sulfate, evaporated, and purified by column chromatography to afford 2-(1-Cyclopropylethyl)-6-methoxy-phenol **(9)** as a colorless oil (3.80 g, 20.8% yield, HPLC: 95.91 %). R_f = 0.4 (petroleum ether/ethyl acetate =100/1). ^{1}H NMR (400MHz, $CDCl_3$): δ 6.92 (dd, *J* = 1.2, 8.0 Hz, 1H), 6.82 (t, *J* = 8.0 Hz, 1H), 6.72 (dd, *J* = 1.2, 8.0 Hz, 1H), 5.69 (s, 1H), 3.86 (s, 3H), 2.47-2.40(m, 1H), 1.31(d, *J* = 7.2 Hz, 3H), 1.05-1.03(m, 1H), 0.56-0.50 (m, 1H), 0.39-0.33 (m, 1H), 0.24-0.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.25, 142.93, 133.21, 119.82, 119.34, 108.10, 55.97, 37.80, 20.39, 17.40, 4.72, 3.92. HRMS (ESI): Calcd. for $C_{12}H_{16}O_2$ $[M+H]^+$: 193.11838. Found: 193.12228.

2-(1-Cyclopropylpropyl)-6-isopropyl-phenol (10): To a stirred solution of 2-(1-cyclopropyl-1-hydroxy-propyl)-6-isopropyl-phenol **(29d)** (3.00 g, 12.80 mmol) and triethylsilane (3.00 g, 25.80 mmol) in DCM (15 mL) was added TFA (11.40 g， 99.98 mmol) dropwise while maintaining the temperature at -30°C. Upon completion of the addition, the reaction mixture was stirred at 0°C for 1 h, and washed with water (20 mL), saturated $NaHCO_3$ (20 mL). After addition of TBAF·$3H_2O$ (2.00 g， 6.34 mmol), the organic phase was stirred for 1 h, washed with water (15 mL×3), brine (15 mL), dried over anhydrous sodium sulfate, evaporated, and purified by column chromatography to afford 2-(1-cyclopropylpropyl)-6-isopropyl-phenol **(10)**

as a colorless oil (1.00 g, 38.0% yield, HPLC: 95.06 %). R_f = 0.5 (petroleum ether/ethyl acetate = 100/1). ^{1}H NMR（400 MHz, $CDCl_3$): δ7.07 (dd, *J* = 1.7, 7.6 Hz, 1H), 7.05 (dd, *J* = 1.7, 7.6 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 4.50 (s, 1H), 3.15 (hept, *J* = 6.8 Hz, 1H), 2.25-2.20 (m, 1H), 1.77-1.75 (m, 2H), 1.26 (d, *J* = 6.8 Hz, 6H), 1.07-1.05 (m, 1H), 0.89 (t, *J* = 7.6 Hz, 3H), 0.62-0.55 (m, 1H), 0.42-0.36 (m, 1H), 0.25-0.19 (m, 1H), 0.10-0.04 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.61, 133.72, 130.59, 125.67, 123.45, 120.36, 44.92, 28.24, 27.18, 22.74, 22.71, 15.67, 12.24, 5.34, 3.04. HRMS (ESI): Calcd. for $C_{15}H_{22}O$ $[M+H]^+$: 219.17042. Found: 219.17425. Anal. Calcd. for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.05; H, 10.20.

2-(1-cyclobutylethyl)-6-isopropylphenol (11): 2-(1-Cyclobutyl-1-hydroxyethyl)-6-isopropyl-phenol **(29e)** (10.40 g, 44.40 mmol) and DCM (100 mL) were added to the flask, followed by the addition of triethylsilane (10.30 g, 88.80 mmol) and 10 min. stirring before it was cooled to -35^{o}C . Trifluoroacetic acid (40.50 g, 355.20 mmol) was slowly added. After being stirred for 40 min., saturated sodium bicarbonate was added to the reaction mixture to adjust the pH value to 7. TBAF·3H_2O (6.94 g, 117.94 mmol) was added to the organic phase, stirring for 2 hrs. The system was washed with saturated sodium chloride and dried with anhydrous sodium sulfate, concentrated under reduced pressure and purified by flash chromatography on silica gel to afford the product **11** as a light yellow oil (8.20 g, 84.5 % yield, HPLC : 96.35%). R_f = 0.35 (petroleum ether). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.96 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.86 (t, *J* = 7.6 Hz, 1H), 4.74 (s, 1H), 3.17 (hept, *J* = 6.8 Hz, 1H), 2.99-2.91 (m, 1H), 2.61-2.55 (m, 1H), 2.19-2.13 (m, 1H), 1.88-1.75 (m, 4H), 1.64-1.58 (m, 1H), 1.28 (d, *J* = 6.8 Hz, 6H), 1.15 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.48, 133.66, 131.09, 124.45, 123.33, 120.50, 41.64, 39.18, 27.48, 27.04, 22.73, 18.23, 17.57. HRMS (ESI): Calcd. for $C_{15}H_{22}O$ [M+H]

$^{+}$: 219.17042. Found: 219.17432. Anal. Calcd. for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.01; H, 10.19.

2-(1-Cyclopentylethyl)-6-isopropyl-phenol (12): To a stirred solution of 2-(1-cyclopentyl-1-hydroxy-ethyl)-6-isopropyl-phenol **(29f)** (3.00 g, 12.08 mmol) and triethylsilane (5.60 g, 48.32 mmol) in DCM (50 mL) was added TFA (11.00 g，96.63 mmol) dropwise at 0^{o}C. Upon completion of the addition, the reaction mixture was stirred at 0^{o}C for 2 h, washed with water (50 mL) and saturated $NaHCO_3$ (50 mL) solution. After the addition of TBAF·$3H_2O$ (1.60 g, 5.07 mmol), the organic phase was stirred for 1 h, washed with water (30 mL), brine (30 mL), dried over anhydrous sodium sulfate, evaporated, and purified by column chromatography to afford 2-(1-Cyclopentylethyl)-6- isopropyl-phenol **(12)** as a colorless oil (2.10 g, 74.7%, HPLC: 95.00 %). R_f = 0.4 (petroleum ether/ethyl acetate = 100/1). ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.04 (dd, J = 1.6, 7.6 Hz, 1H), 7.02 (dd, J = 1.6, 7.6 Hz, 1H), 6.87 (t, J = 7.6 Hz, 1H), 4.72 (s, 1H), 3.18-3.11 (m, 1H), 2.78-2.74 (m, 1H), 2.07-2.04 (m, 1H), 1.92-1.90 (m, 1H), 1.69-1.63 (m, 1H), 1.59-1.43 (m, 4H), 1.27-1.25 (m, 10H), 1.09-1.01 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.04, 133.69, 132.86, 124.93, 123.10, 120.48, 46.73, 38.51, 31.58, 31.52, 27.25, 25.44, 25.17, 22.75, 22.73, 20.45. HRMS (ESI): Calcd. for $C_{16}H_{24}O$ $[M+H]^{+}$: 233.18607. Found: 233.19003.

2-(Dicyclopropylmethyl)-6-isopropyl-phenol (13): To a stirred solution of 2-[dicyclopropyl(hydroxy)methyl]-6-isopropyl-phenol (**29g**) (2.00 g, 8.12 mmol) and triethylsilane (1.90 g, 16.34 mmol) in DCM (10 mL) was added TFA (3.70 g，32.45 mmol) dropwise at -10 ^{o}C. Upon completion of the addition, the reaction mixture was stirred at -10 ℃ for 3 hrs, and

washed with water (10 mL), saturated $NaHCO_3$ (aq, 10 mL). The organic phase was added TBAF·$3H_2O$ (1.30 g, 4.12 mmol), stirred for 2 hrs, washed with water (15 mL × 3), brine (15 mL), dried over anhydrous sodium sulfate, evaporated and purified by column chromatography to afford 2-(dicyclopropylmethyl) -6-isopropyl-phenol **(13)** as a colorless oil (0.2 g, 11.0%, HPLC: 95.40 %). R_f = 0.5 (petroleum ether/ethyl acetate = 50/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (dd, *J* = 1.6, 7.6 Hz, 1H)), 7.06 (dd, *J* = 1.6, 7.6 Hz, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 5.10 (s, 1H), 3.19 (hept, *J* = 6.9 Hz, 1H), 2.06 (t, *J* = 7.6 Hz, 1H), 1.26(d, *J* = 6.9 Hz, 6H), 1.15-1.11 (m, 2H), 0.62-0.55 (m, 2H), 0.46-0.39 (m, 2H), 0.34-0.28 (m, 2H), 0.18-0.12 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.73, 134.14, 129.68, 126.44, 123.90, 120.25, 46.36, 27.10, 22.70, 14.88, 4.44, 2.71. HRMS (ESI): Calcd. for $C_{16}H_{22}O$ $[M+H]^+$: 231.17042. Found: 231.17428.

2-**(1-Cyclopropylethyl)-6-(1-cyclopropylpropyl)phenol (14)**: To a stirred solution of 2-(1-cyclopropylethyl)-6-(1-cyclopropyl-1-hydroxy-propyl)phenol **(23b)** (0.80 g, 3.07mmol) and triethylsilane (0.89 g, 7.68 mmol) in 30mL dichloromethane was added dropwise TFA (0.88 g, 7.68 mmol) below 0^{o}C under nitrogen atmosphere. Upon completion of the addition, the reaction mixture was stirred for 3h at 0^{o}C. The reaction solution was quenched with 100 mL ice-water and extracted with dichloromethane (30 mL×2), The combined organic layers were treated with TBAF·$3H_2O$ (0.80 g，3.07 mmol) and stirred for 30 min at ambient temperature. The mixture was added to 100mL water and extracted with dichloromethane (30 mL×3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography to give the title compound **14** (0.45 g, 59.93% yield, HPLC: 98.52%)) as a pale yellow oil. R_f = 0.5 (petroleum ether/ethyl acetate = 50/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (d, *J* = 7.6 Hz, 1H),

7.07-7.04 (m, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 4.93 (s, 1H), 2.54-2.51 (m, 1H), 2.27-2.21 (m, 1H), 1.82-1.70 (m, 2H), 1.30 (d, *J* = 7.6 Hz, 3H), 1.09-1.02 (m, 2H), 0.89 (t, *J* = 7.6 Hz, 3H), 0.59-0.52 (m, 2H), 0.48-0.35 (m, 2H), 0.25-0.05 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.02, 131.86, 131.79, 130.87, 130.80, 124.97, 120.22, 44.82, 37.02, 37.00, 28.36, 28.23, 19.99, 15.66, 15.22, 5.37, 5.32, 4.24, 3.62, 3.56, 3.01, 2.96. HRMS (ESI): Calcd. for $C_{17}H_{24}O$ $[M+H]^+$: 245.18607. Found: 245.18992. Anal. Calcd. for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.13; H, 9.94.

2-(1-Cyclopropyl-2-methylpropyl)-6-(1-cyclopropylethyl)phenol (15) : To a stirred solution of 2-(1-cyclopropylethyl)-6-(1-cyclopropyl-1-hydroxy-2-methyl-propyl)phenol **(23c)** (0.80 g, 2.92 mmol) and triethylsilane (0.85 g, 7.29 mmol) in 30 mL dichloromethane was added dropwise TFA (0.83 g, 7.29 mmol) below 0^{o}C under a nitrogen atmosphere. Upon completion of the addition, the reaction mixture was stirred for 3h at 0^{o}C. The reaction solution was quenched with 100 mL ice-water and extracted with dichloromethane (30 mL×2), To the combined organic layers were treated TBAF·$3H_2O$ (0.76 g, 2.92 mmol) and the mixture stirred for 30 min at ambient temperature. The mixture was diluted with 100 mL water and extracted with dichloromethane (30 mL×3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography to give the title compound **15** (0.50 g, 66.16% yield, HPLC: 97.59%) as a pale yellow oil. R_f = 0.6 (petroleum ether/ethyl acetate = 50/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10-7.09 (m, 1H), 7.06-7.03 (m, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 4.82 (s, 1H), 2.57-2.51 (m, 1H), 2.07-2.01 (m, 1H), 2.01-1.92 (m, 1H), 1.30 (d, *J* = 7.2 Hz, 3H), 1.09-1.00 (m, 5H), 0.85 (d, *J* = 6.8 Hz, 3H), 0.70-0.64 (m, 1H), 0.57-0.52 (m, 1H), 0.48-0.41 (m, 1H), 0.36-

0.12 (m, 4H), -0.04-0.10 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.88, 131.50, 131.34, 131.29, 126.43, 124.72, 124.69, 120.05, 50.79, 50.73, 36.93, 36.79, 33.99, 33.83, 21.56, 21.50, 20.64, 19.93, 19.88, 16.89, 16.83, 13.89, 13.87, 7.92, 7.89, 4.18, 4.14, 3.55, 3.36, 2.58, 2.53. HRMS (ESI): Calcd. for $C_{18}H_{26}O$ $[M+H]^+$: 259.20172. Found: 259.20558.

2-(1-Cyclopropylethyl)-6-(dicyclopropylmethyl)phenol (16): To a stirred solution of 2-(1-cyclopropylethyl)-6-[dicyclopropyl(hydroxy)methyl]phenol **(23d)** (0.80 g, 2.94 mmol) and triethylsilane (0.85 g, 7.34 mmol) in 30mL dichloromethane was added dropwise TFA (0.84 g, 7.34 mmol) below 0^{o}C under a nitrogen atmosphere. Upon completion of the addition, the reaction mixture was stirred for 3h at 0^{o}C. The reaction solution was quenched with 100 mL of ice-water and extracted with dichloromethane (30 mL×2), To the combined organic layers was added TBAF·3H_2O (0.77 g， 2.94 mmol) and the mixture stirred for 30 min at ambient temperature. The mixture was diluted with 100mL water and extracted with dichloromethane (30 mL×3). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography to give the title compound **16** (0.50 g, 66.31% yield, HPLC: 98.49%) as a pale yellow oil. R_f = 0.5 (petroleum ether/ethyl acetate = 50/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.14 (dd, J = 1.6, 7.6 Hz, 1H), 7.11 (dd, J = 1.6, 7.6 Hz, 1H), 6.88 (t, J = 7.6 Hz, 1H), 5.20 (s, 1H), 2.53-2.50 (m, 1H), 2.10-2.05 (m, 1H), 1.29 (d, J = 6.8 Hz, 3H), 1.17-1.12 (m, 2H), 1.08-1.02 (m, 1H), 0.58-0.52 (m, 3H), 0.47-0.38 (m, 3H), 0.33-0.27 (m, 2H), 0.22-0.17 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.03, 132.44, 129.84, 126.55, 125.32, 120.13, 46.21, 37.15, 20.10, 17.05, 14.93, 14.90, 4.43, 4.40, 4.36, 3.70, 2.68, 2.63. HRMS (ESI): Calcd. for $C_{18}H_{24}O$ $[M+H]^+$:

257.18607. Found: 257.18990. Anal. Calcd. for $C_{18}H_{24}O$: C, 84.32; H, 9.44. Found: C, 84.52; H, 9.59.

Preparation of prodrugs:

[[2-(1-Cyclopropylethyl)-6-sec-butyl-phenoxy]methyl-sodiooxy-phosphoryl]oxy-sodium (Pro-1) or its isomers: To a solution of phosphoric acid (85% aq., 5.10 g，71.10 mmol) in acetonitrile (50 mL) was added triethylamine (9.00 g，89.95 mmol) at room temperature. The solution was then heated to 60°C for 30min, followed by the addition of the corresponding isomer of 2-(1-cyclopropylethyl)-6-sec-butylphenol chloromethylether (2.37 g, 8.90 mmol) in acetonitrile (10mL), stirring for another 2 hrs at 60°C. The reaction mixture was concentrated, acidified with 10% HCl to pH = 1 and extracted with MTBE (30 mL× 3). The combined organic layers was alkalized with 10% NaOH to pH = 10. The aqueous phase was washed with MTBE (10 mL× 3), concentrated under reduced pressure to give the **Pro-1** or its isomers (3.04 g, 97.15% yield) as white powder.

[[2-(1-Cyclopropylethyl)-6-sec-butyl-phenoxy]methyl-sodiooxy-phosphoryl]oxy-sodium (Pro-1): HPLC: 95.60%; ^{1}H NMR (400 MHz, D_2O): δ 7.42-7.37 (m, 1H), 7.31-7.25 (m, 2H), 5.22-5.20 (m, 2H), 3.23-3.16 (m,1H), 2.70-2.64 (m,1H), 1.68-1.54 (m, 2H), 1.35-1.29 (m, 3H), 1.26-1.20 (m, 3H), 1.10-0.99 (m, 1H), 0.85-0.78 (m, 3H), 0.59-0.53 (m, 1H), 0.37-0.27 (m, 2H), 0.17-0.11 (m, 1H). MS m/z (ESI): 327.1 $[M-2Na+H]^-$.

[[2-[(1*R*)-1-Cyclopropylethyl]-6-[(1*R*)-1-methylpropyl]phenoxy]methoxy-sodiooxy-phosphoryl]oxysodium Pro-(*R*, *R*)-1 or **[[2-[(1*S*)-1-cyclopropylethyl]-6-[(1*S*)-1-**

methylpropyl]phenoxy]methoxy-sodiooxy-phosphoryl]oxysodium Pro-(*S, S*)-1: HPLC: **Pro-(*R, R*)-1**, 98.60%; **Pro-(*S, S*)-1**, 94.46%.^{1}H NMR (400 MHz，D_2O): δ 7.35 (dd, *J* = 2.1, 7.6 Hz, 1H), 7.23 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.20 (dd, *J* = 2.1, 7.6 Hz, 1H), 5.14 (q, *J* = 3.7 Hz, J_{PH} = 6.3 Hz, 1H), 5.13 (q, *J* = 3.7 Hz, J_{PH} = 6.3 Hz, 1H), 3.23-3.18 (m, 1H), 2.72-2.64 (m, 1H), 1.72-1.59 (m, 2H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.23 (d, *J* = 6.8 Hz, 3H), 1.13-1.07 (m, 1H), 0.86 (t, *J* = 7.2 Hz, 3H), 0.61-0.58 (m, 1H), 0.41-0.33 (m, 2H), 0.22-0.16 (m, 1H). MS m/z (ESI): 327.1 [M-2Na+H]$^-$.

[[2-[(1*R*)-1-Cyclopropylethyl]-6-[(1*S*)-1-methylpropyl]phenoxy]methoxy-sodiooxy-phosphoryl]oxysodium Pro-(*R,S*)-1 or [[2-[(1*S*)-1-cyclopropylethyl]-6-[(1*R*)-1-methylpropyl]phenoxy]methoxy-sodiooxy-phosphoryl]oxysodium Pro-(*S,R*)-1:

HPLC: **Pro-(*R, S*)-1**, 95.00%; **Pro-(*S, R*)-1**, 97.89%. ^{1}H NMR (400 MHz, D_2O): δ 7.40 (dd, *J* = 2.0, 7.3 Hz, 1H), 7.31 (dd, *J* = 7.3, 7.6 Hz, 1H), 7.27 (dd, *J* = 2.0, 7.6 Hz, 1H), 5.21 (d, J_{PH} = 6.4 Hz, 2H), 3.23-3.16 (m, 1H), 2.72-2.65 (m, 1H), 1.68-1.57 (m, 2H), 1.36 (d, *J* = 6.8 Hz, 3H), 1.25 (d, *J* = 6.8 Hz, 3H), 1.08-1.00 (m, 1H), 0.80 (t, *J* = 7.2 Hz, 3H), 0.59-0.54 (m，1H), 0.33-0.26 (m，2H), 0.16-0.09 (m，1H). MS m/z (ESI): 327.1 [M-2Na+H]$^-$.

[[2,6-Bis[(1*R*)-1-cyclopropylethyl]phenoxy]methoxy-sodiooxy-phosphoryl]oxysodium Pro-(*R,R*)-2 and **[[2-[(1*R*)-1-cyclopropylethyl]-6-[(1*S*)-1-cyclopropylethyl]phenoxy]methoxy-sodiooxy-phosphoryl]oxysodium Pro-(*R,S*)-2** and **[[2,6-bis[(1*S*)-1-cyclopropylethyl]phenoxy]methoxy-sodiooxy-phosphoryl]oxysodium Pro-(*S,S*)-2**: A stirred solution of Phosphorous acid (2.25 g, 22.95 mmol) and TEA (2.90 g, 28.69 mmol) in CH_3CN (10

mL) was stirred at 60°C for 0.5 h, followed by the addition of 2-(chloromethoxy)-1,3-bis[(1R)-1-cyclopropylethyl]benzene **(*R*,*R*)-31** or 2-(chloromethoxy)-1-[(1R)-1-cyclopropylethyl]-3-[(1S)-1-cyclopropylethyl]benzene **(*R*,*S*)-31** or 2-(chloromethoxy)-1,3-bis[(1S)-1-cyclopropylethyl]benzene **(*S*,*S*)-31** (0.80 g, 2.87 mmol). The reaction mixture was heated to 75°C, and stirred at this temperature for another 2 hrs, concentrated, and washed with water (20 mL). The aqueous phase was adjusted by HCl (10 %) to pH = 1, extracted by MTBE (20 mL × 3). The organic phase was combined, mixed with water (20 mL), adjusted by NaOH (18%) to pH = 10-11, and separated in funnel. The aqueous phase was washed by MTBE (30 mL ×4), and then evaporated. The residue was diluted with CH_3CN (50 mL), and stirred at 50°C for 0.5 h and filtered to afford the title compound (0.60 g, 54.41% yield, HPLC; 97.32%) as a white solid. ^{1}H NMR (400 MHz, D_2O): δ 7.45 (d, J = 7.6 Hz, 2H), 7.32 (t, J = 7.6 Hz, 1H), 5.17 (q, J = 3.7 Hz, J_{PH} = 10.5 Hz, 1H), 5.15 (q, J = 3.7 Hz, J_{PH} = 10.5 Hz, 1H), 2.66-2.62 (m, 2H), 1.31 (d, J = 6.8 Hz, 6H), 1.12-1.09 (m, 2H), 0.63-0.58 (m, 2H), 0.32-0.30 (m, 4H), 0.19-0.15 (m, 2H).

[[2-[(1*S*)-1-cyclopropylethyl]-6-isopropyl-phenoxy]methyl-sodiooxy-phosphoryl]oxy-sodium Pro-(*S*)-6 and **[[2-[(1*R*)-1-cyclopropylethyl]-6-isopropyl-phenoxy]methyl-sodiooxy-phosphoryl]oxysodium Pro-(*R*)-6**: A stirred solution of Phosphorous acid (31.60 g, 0.32 mol) and TEA (40.50 g, 0.40 mol) in CH_3CN (100 mL) was stirred at 60°C for 0.5 hr, followed by the addition of 2-(chloromethoxy) -1-[(1*S*)-1-cyclopropylethyl]-3-isopropyl-benzene **(*S*)-32** or 2-(chloromethoxy)-1-[(1*R*)-1-cyclopropylethyl]-3-isopropyl-benzene **(*R*)-32** (10.00 g, 0.04 mol). The reaction mixture was heated to 75°C, and stirred at this temperature for another 2 hrs, concentrated, and mixed with water (100 mL). The aqueous phase was adjusted with HCl (10%) to pH=1, extracted by MTBE (100 mL × 3). The organic phase was combined, mixed with water

(100 mL), adjusted with NaOH (18%) to pH=10-11, and separated. The aqueous phase was washed by MTBE (50 mL × 4), and then evaporated. The residue was diluted with CH_3CN (50 mL), and stirred at 50°C for 0.5 h and filtered to afford the title compounds (4.20 g, 76% yield, HPLC: 99.91%) as white solid. ^{1}H NMR (400 MHz, D_2O): δ 7.45 (dd, J = 2.4, 7.1 Hz, 1H), 7.35 (dd, J = 7.1, 7.7 Hz, 1H), 7.32 (dd, J = 2.4, 7.7 Hz, 1H), 5.25 (q, J = 3.9 Hz, J_{PH} = 9.9 Hz, 1H), 5.22 (q, J = 3.9 Hz, J_{PH} = 9.9 Hz, 1H), 3.49 (hept, J = 6.9 Hz, 1H), 2.68-2.62 (m, 1H), 1.34 (d, J = 7.0 Hz, 3H), 1.28 (d, J = 6.9 Hz, 3H), 1.25 (d, J = 6.9 Hz, 3H), 1.07-1.04 (m, 1H), 0.60-0.58 (m, 1H), 0.37-0.33 (m, 2H), 0.17-0.15 (m, 1H). MS m/z (ESI): 313.2 $[M-2Na+1]^-$.

ASSOCIATED CONTENT

Supporting Information Available: Preparation and characterization data for compounds **1-32** and prodrugs of compounds 1, 2 and 6**.** This material is available free of charge via the internet at http://pubs.acs.org.

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CONFLICTS OF INTERESTS

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

ABBREVIATIONS USED

DMF, N,N-dimethylformamide; DCM, dichloromethane; $NaHCO_3$, sodium hydrogen carbonate; TFA, trifluoroacetic acid; THF, tetrahydrofuran; MeOH, methanol; TFAA, trifluoroacetic anhydride; DMSO, dimethyl sulfoxide; Et_3N, triethylamine; p-TsOH, toluene-p-sulfonic acid; K_2CO_3, potassium carbonate; TBAF, tetrabutylammoniumfluorid; Et_2O, Ethylether; KOH, potassium hydrate; MTBE, methyl tert-butyl ether; DIAD, Diisopropyl azodicarboxylate; EA, ethyl acetate; Pet, petroleum ether; $NaHCO_3$, sodium bicarbonate;

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