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# Design, synthesis, and characterization of BK channel openers based on oximation of abietane diterpene derivatives

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ABSTRACT

Oxime ether derivatives at the benzylic position of unsubstituted, dichloro, trichloro, and monobromo derivatives of the aromatic C-ring of dehydroabietic acid and podocarpic acid were synthesized and evaluated as BK channel openers in an assay system of CHO-K1 cells expressing hBKα channels. Detailed SAR analysis showed that the oximation was particularly effective in the cases of dehydroabietic acid derivatives, and some of these oxime derivatives showed more potent BK channel activities than the standard compound, NS1619. The present studies provide a new structural basis for development of efficient BK channel openers.



## 1. Introduction

Potassium ($K^+$) channels are a structurally diverse family of transmembrane proteins that are modulated by voltage, cell metabolism, and calcium or receptor-mediated processes. They play a key role in the regulation of membrane potential, and in excitable cells they regulate the frequency and form of the action potential, the release of neurotransmitters, and contractility.[1–3] Calcium-activated potassium ($K_{Ca}$) channels are a subgroup of these channels that share a dependence on intracellular calcium ion concentration for activity and are, in addition, regulated by membrane potential and phosphorylation state.[4] On the basis of single-channel conductance, the $K_{Ca}$ channels are further subdivided into three types, BK (maxi-K), IK, and SK channels, referring to large (100–300 picosiemens, (pS)), intermediate (25–100 pS), and small conductance (2–25 pS) $K_{Ca}$ channels, respectively. These channels vary in pharmacology, distribution and function, as well as in sensitivity to voltage and $Ca^{2+}$ concentration: that is, BK channels show voltage-dependency, while IK and SK channels are voltage-independent. BK channels are of particular interest because of their large channel conductance and their expression in a range of excitable cell types, including neurons and smooth muscle cells.[5]

BK channels are uniquely regulated by changes in both transmembrane potential and intracellular $Ca^{2+}$ level,[6] and may couple with other ion channels (such as $Ca^{2+}$ ion channels,[7,8] chloride channel,[9] TRPC channels[10]) to serve as a negative feedback pathway controlling ionic homeostasis, cell excitability, and neuron activity.[11] Structurally, BK channels consist of channel-forming α-subunits and accessory β-subunits arranged in tetramers,[12] having a voltage sensor and pore as the membrane-spanning domain and having a cytosolic domain containing metal-binding sites. Recently published studies on electron cryomicroscopy (cryo-EM)[13] and X-ray crystallographic structure analysis[14] of the BK channel have provided the first glimpse into the assembly of the quaternary structure of this massive channel protein, corroborating the close interactions among these domains during channel gating that were suggested by the previous functional studies.[15] Cloning studies have revealed the presence of multiple splice variants of α-subunits and multiple subtypes of β-subunits ($\beta_1$, $\beta_2/\beta_3$, and $\beta_4$),[16] which may be specific to tissues, organs and functions (e.g., $\beta_1$: smooth muscle, $\beta_4$: brain).[17] Because of the large conductance, significant dependency on intracellular $Ca^{2+}$ concentration, and potential organ selectivity due to the variety of β subunits, control of opening of BK channels is a potentially powerful intervention in the modulation of muscle contractility or neurotransmitter release and hormone secretion. Openers of these channels have emerged as potentially useful agents in the therapy of various disease states associated with both the central nervous system and smooth muscle, such as acute stroke, epilepsy, psychoses, erectile dysfunction, arterial hypertension, asthma, and bladder hyperactivity.[18,19] Well-characterized BK channel openers not only are

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expected to have therapeutic potential, but also should be of assistance in elucidating the function, structure and role of BK channels.

The range of synthetic and naturally occurring compounds that exhibit BK channel-opening activity, together with the electrophysiological and biochemical pharmacological properties of these compounds, has recently been reviewed.[20] Synthetic benzimidazolone derivatives, represented by NS004 and NS1619 (Chart 1), were the first BK channel openers to be discovered, and have been the most widely used pharmacological tools in investigations of the function of BK channels, as well as having been lead compounds for the design of several novel synthetic BK openers. Biaryl amines, such as mefenamic and flufenamic acids, biarylureas (NS1608), biarylthioureas (NS11021), aryloxindoles (BMS-204352), arylpyrroles (NS-8), and indole-3-carboxylic acid esters (CGS-7184 and CGS-7181) have also been described and characterized as BK channel openers. In addition to these synthetic compounds, a number of compounds derived from natural products have been evaluated as BK channel openers, including dehydrosoyasaponin-I (DHS-I), L-735334, bile acids and diterpenes such as maxikdiol (Chart 1). However, the range of scaffolds for the molecular design of BK channel openers is still limited and the BK channel-opening potency of currently available compounds is rather weak.

Our pioneering work on pimarane compounds, which have an intuitive structural similarity to maxikdiol, has revealed that pimaric acid (Chart 1) is a potent BK channel opener.[21] Other diterpene analogues, such as abietic acid, sclareol and methyl pimarate, do not display significant ability to activate BK channels, despite their chemical structural similarity. On the other hand, dehydroabietic acid (DHAA, **1a**, Chart 1), which is structurally related to non-aromatic abietic acid, showed weak but definite BK channel-opening activity.[22] Chemical modification of DHAA by introduction of halogen atoms on the benzene ring to afford 12,14-dichlorodehydroabietic acid (diCl-DHAA, **1b**) markedly increased the BK channel-opening activity.[22] All these BK channel openers are assumed to interact with the α subunit of the BK channels.[23] Using DHAA and diCl-DHAA as starting points, a number of derivatives, wherein the C ring was modified by introduction of divergent substituents, have been synthetically prepared and some of them have been characterized as BK channel openers.[24] Also, we found that podocarpic acid (**2**), structurally closely related to dehydroabietic acid, but bearing the carboxylic acid functionality in a reverse stereochemistry, represents a new scaffold for BK channel openers.[25] Pimaric acid, dehydroabietic acid and podocarpic acid are diterpenes of the abietane chemical class, with common 3-ring phenanthrene structures. However, modification of the B ring of these novel tricyclic compounds has been little explored.[26] In a recent study, we synthesized a series of oxime and oxime ether derivatives of the benzylic ketone of diCl-DHAA and found that the oxime ether structure significantly increased the BK channel-opening activity of diCl-DHAA.[27]

In this paper, we describe detailed SAR studies of introduction of oximate at the benzylic position of the B ring of dehydroabietic acid and podocarpic acid derivatives with general structures **3** and **4**, and validate the effectiveness of the oximation strategy for enhancing BK channel-opening activity.

## 2. Chemistry

### 2.1. Dehydroabietic acid derivatives

Initially, we synthesized a series of oxime (**3a**) and oxime ether derivatives (**3b**–**m**) of the benzylic ketone of diCl-DHAA (**1b**). The four synthetic routes used to access the target compounds **3a**–**m** are summarized in Schemes 1–4. The parent oxime **3a** was synthesized as shown in Scheme 1. Benzylic oxidation of the methyl ester derivative **1c** with $CrO_3$ in $AcOH/Ac_2O$ afforded the 7-keto derivative **1d**. Treatment of the ketone **1d** with hydroxylamine hydrochloride in EtOH and pyridine under heating at reflux afforded the corresponding *E*-oxime **5a** (*anti*) as the sole isolated product. The *E*-stereochemistry was confirmed by a single-crystal structure analysis.[27] Finally, the methyl ester of **5a** was hydrolyzed with KOH in methanol in the presence of 18-crown-6 to give the desired carboxylic acid **3a**. Compound **3b** was obtained by condensation of ketone intermediate **1d** with methoxylamine hydrochloride, followed by hydrolysis of the methyl ester with KOH and 18-crown-6 in methanol.

Compounds **3f**, **3g**, and **3m** were obtained by O-alkylation of the oxime **5a** with various alkyl bromides (allyl bromide, propargyl bromide and benzyl bromide, respectively) under basic conditions (KOH) in a mixture of $H_2O$–$CH_2Cl_2$ in the presence of TBAB, followed by basic hydrolysis of the methyl ester to the carboxylic acid with KOH in MeOH in the presence of 18-crown-6 by heating at reflux, as depicted in Scheme 2. The latter hydrolysis step of the methyl ester to the acid proceeded very slowly. Compounds **3d**, **3e**, and **3i**–**l** were synthesized by O-alkylation of the oxime oxygen atom in a similar manner. According to the literature,[28] $KOBu^t$ in DMSO can hydrolyze hindered esters. The desired acid compounds **3d**, **3e**, and **3i**–**l** were obtained by using these hydrolysis conditions at room temperature for 40 min (Scheme 3).

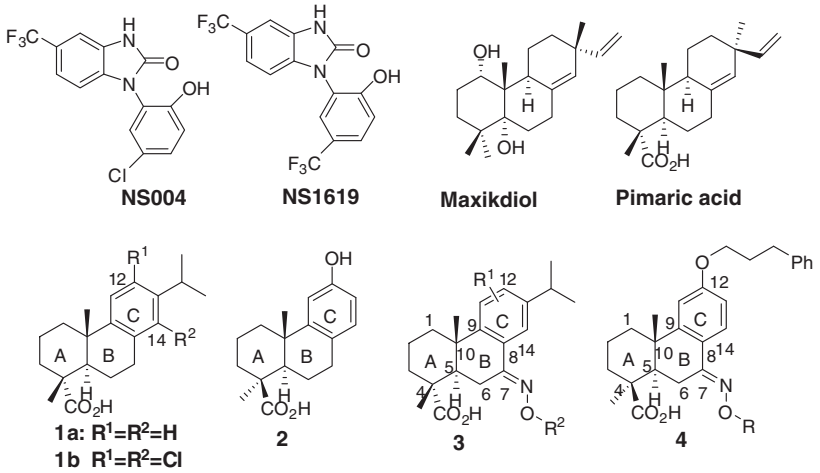
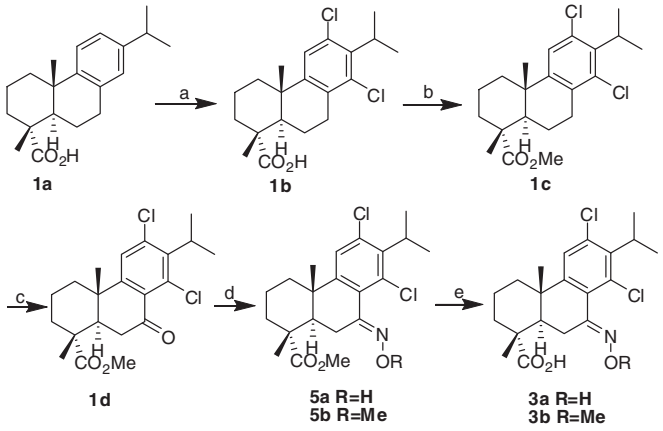
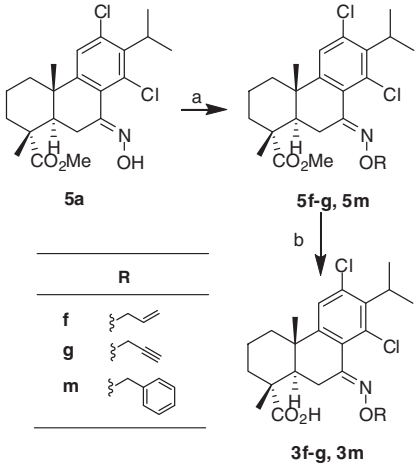


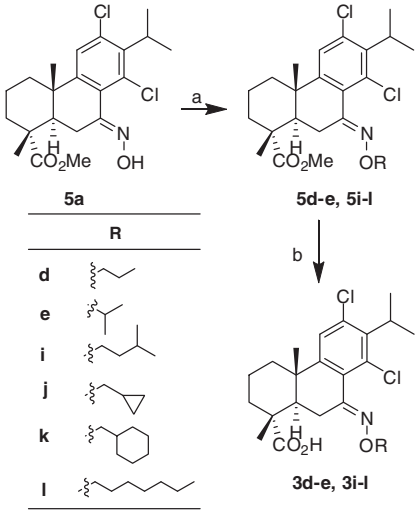

Chart 1.



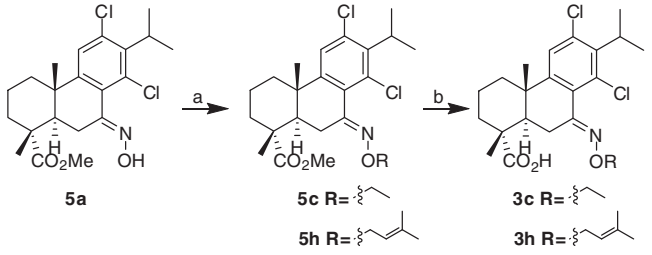

**Scheme 1.** Reagents and conditions: (a) $Cl_2$, $FeCl_3/SiO_2$, $DDQ/SiO_2$, $CCl_4$, 39%; (b) $TMSCHN_2$, MeOH–toluene, rt, 90%; (c) $CrO_3$, $AcOH/Ac_2O$, 58%; (d) $NH_2OR{\cdot}HCl$, EtOH, Py, reflux, 87% (R = H) and 100% (R = Me); (e) KOH, 18-crown-6, MeOH, reflux, 88% (R = H) and 79% (R = Me).




**Scheme 2.** Reagents and conditions: (a) RBr, TBAB, 1 N KOH, $CH_2Cl_2$, 40 °C, 60–89%; (b) KOH, 18-crown-6, MeOH, reflux, 43–85%.



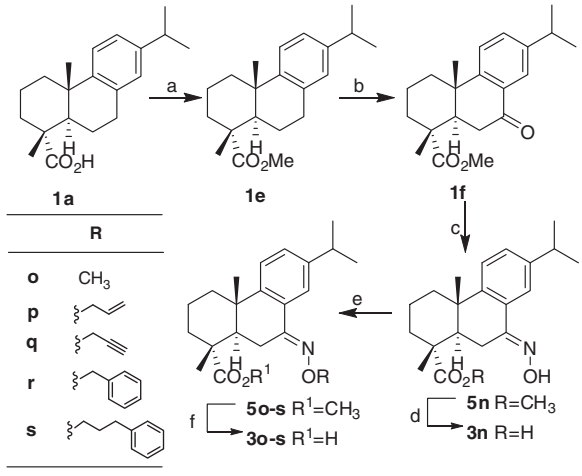

**Scheme 3.** Reagents and conditions: (a) RBr, NaH, DMF, 0 °C to rt, 61–86%; (b) $KOBu^t$, DMSO, rt, 24–63%.




**Scheme 4.** Reagents and conditions: (a) RBr, NaH, DMF, 0 °C to rt, 56% (**5c**) and 83% (**5h**); (b) KOH, 18-crown-6, MeOH, microwave irridiation, 145 °C, 57% (**3c**) and 63% (**3h**).

Alkylation of the oxime intermediate **5a** with 3,3-dimethylallyl bromide after deprotonation of the oxime hydroxy group of **5a** with NaH afforded the intermediate **5h**. However, basic hydrolysis of the methyl ester with KOH in the presence of crown ether by heating at reflux failed, probably because of steric hinderance of the methyl ester. Moreover, alternative hydrolysis conditions involving $KOBu^t$ in DMSO led to decomposition to the product **3a**. One possibility is that the olefin ether (allyl ether) was first isomerized to the vinyl ether by the action of $KOBu^t$ in DMSO and the latter decomposed under the acidic work-up conditions.[29] Finally, the desired compound **3h** was obtained in 63% yield by hydrolysis of **5h** with KOH in MeOH in the presence of 18-crown ether-6 under microwave irradiation at 145 °C for 1 h. Compound **3c** was obtained similarly (Scheme 4).

To investigate further the effects of substituents in ring C on the activity, we synthesized oxime and oxime ether derivatives of the benzylic ketone of DHAA, 12-bromo-DHAA (12-Br-DHAA), and 11,12,14-trichlorodehydroabietic acid (triCl-DHAA). For the synthesis of the DHAA series of compounds, the parent oxime **5n** was synthesized as shown in Scheme 5. Benzylic oxidation of the methyl ester derivative **1e** with $CrO_3$ in $AcOH/Ac_2O$ afforded the 7-keto derivative **1f** in moderate yield. Similarly, treatment of the ketone **1f** with hydroxylamine hydrochloride in EtOH and pyridine by heating under reflux afforded the corresponding *E*-oxime **5n** (*anti*) as the sole isolated product. The desired carboxylic acid **3n** was obtained by hydrolysis of the methyl ester of **5n** with $KOBu^t$ in DMSO. O-Alkylation of the oxime **5n** with various alkyl bromides and subsequent basic hydrolysis of the methyl ester with KOH in MeOH in the presence of crown ether by heating under




**Scheme 5.** Reagents and conditions: (a) concd $H_2SO_4$, MeOH, 85 °C, 91%; (b) $CrO_3$, $AcOH/Ac_2O$, 48%; (c) $NH_2OH{\cdot}HCl$, EtOH, Py, reflux, 79%; (d) $KOBu^t$, DMSO, rt, 79%; (e) RBr, NaH, DMF, 0 °C to rt, 70–92%; (f) KOH, 18-crown-6, MeOH, reflux, 57–93%.

reflux afforded compounds **3o–s**, respectively, as depicted in Scheme 5.

Regioselective bromination of **1e** with NBS in $CH_3CN$ in the presence of Montmorillonite K-10 afforded a mixture of 12- and 14-monobromo derivatives **1g** and **1h** in a ratio of 3.1:1. Starting from the key intermediate **1g**, the desired acid derivatives **3t–v** were synthesized according the procedure shown in Scheme 6.

Furthermore, we synthesized the oxime and oximate derivatives of 11,12,14-trichlorodehydroabietic acid (triCl-DHAA). By controlling the amount of $Cl_2$ and the reaction time, trichlorinated DHAA (**1j**) can be obtained in 35% yield. As shown in Scheme 1, compounds **3w–y** were similarly obtained in moderate overall yields (Scheme 7).

Also, we synthesized the ketone derivatives (**1m**, **1n** and **1p**) to confirm the importance of the oximic group for BK channel-opening activity. As shown in Scheme 8, direct benzylic oxidation of the carboxylic acid **1b** with $CrO_3$ in $Ac_2O$/AcOH afforded 7-oxo-12,14-dichlorodehydroabietic acid **1m** in 36% yield. Compounds **1n** and **1p** were obtained by hydrolysis of the corresponding methyl esters with KOBu$^t$ in DMSO at rt after benzylic oxidation (**1f** and **1i**).

### 2.2. Podocarpic acid derivatives

Prior to the benzylic oxidation, the 12-phenol group of compound **6a** was firstly protected as an acetate intermediate (**6b**), and then oxidized with chromium trioxide to afford the 7-oxo derivative **6c** in 85% yield (Scheme 9). During condensation of **6c** with hydroxylamine hydrochloride in the presence of pyridine by heating at 100 °C for 3 h, a part of the 12-acetoxy group was removed, and a mixture of two intermediates **6d** and **6e** was obtained. When a longer heating time of 17 h was applied in the oximation process, the acetate was completely hydrolyzed to give the phenol derivative, as in the case of oximation of **6c** with *O*-methylhydroxyamine hydrochloride, yielding the deprotected compound **6f**, as depicted in Scheme 9.

Alkylation of **6e** with an excess of 1-bromo-3-phenylpropane gave a mixture of compounds, O,O-dialkylated **6g** and O-monoalkylated **6h** (Scheme 10). Subsequent hydrolysis of isolated **6h** with KOBu$^t$ in DMSO at 60 °C afforded the desired compound **4a**. On the other hand, hydrolysis of **6g** with KOBu$^t$ in DMSO at 60 °C afforded no desired carboxylic acid product **4g**, instead an unexpected new compound, the 6-hydroxy acid derivative **6i**, was generated. Hydrolysis of **6g** with KOH in MeOH in the presence of 18-crown-6-ether under microwave irradiation at 145 °C for 1 h or up to 5 h resulted in practically no reaction; when the reaction was carried out under microwave irradiation overnight, **6g** decomposed without formation of the desired product. In the similar synthesis of **4b**, this unexpected hydroxylation occurred in the hydrolysis step of the ester to the acid: O-alkylation of **6f** with 1-bromo-3-phenylpropane gave compound **6j**, and then hydrolysis of **6j** with KOBu$^t$ in DMSO at 60 °C afforded a mixture of the desired **4b** as a minor product and the major by-product **6k**. We also studied the BK channel-opening activities of these hydroxylated carboxylic acids (**6i** and **6k**). The *O*-methyl compound **7a** was also obtained by direct basic hydrolysis of the ester **6f** (Scheme 10).

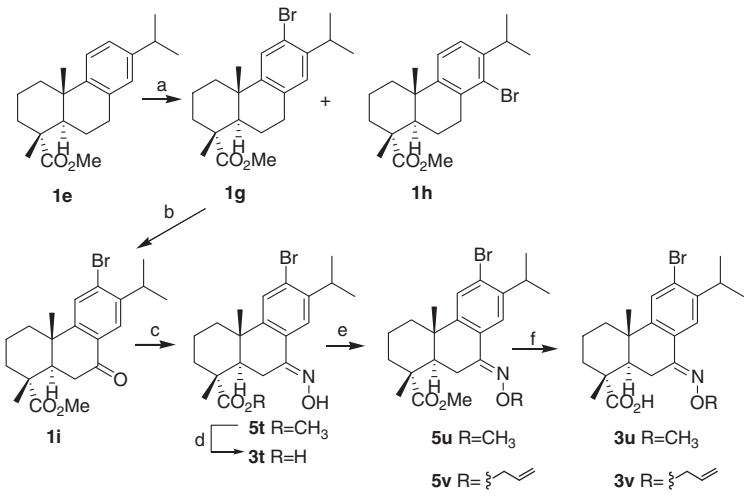
The synthetic route involving initial alkylation of the oxime hydroxyl group of the ester, followed by basic hydrolysis of the ester to the acid, was accompanied with unexpected hydroxylation. In order to avoid this hydroxylation reaction, the synthetic route was modified, beginning with hydrolysis of the ester **6h** to the acid intermediate **4a**, followed by selective O-alkylation of the oxime hydroxyl functionality to afford the desired compounds in moderate conversion yields (Scheme 11).

## 3. Results and discussion

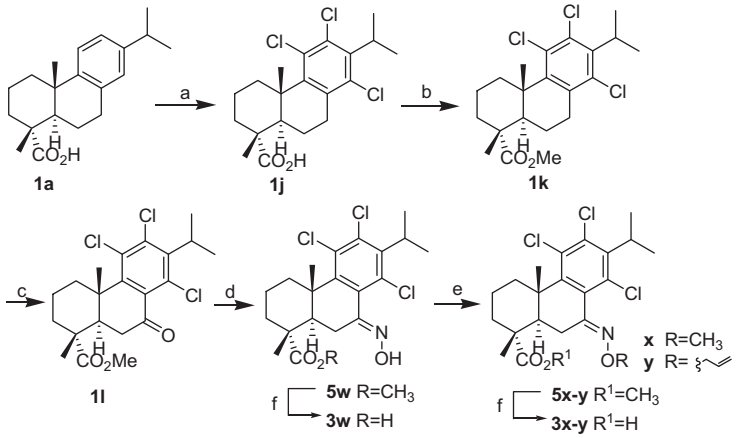
The activities of all the target compounds as BK channel modulators were evaluated by means of automated patch clamp recording using the 64-hole Population Patch Clamp (PPC) technique.[30,31] The BK channel was activated by applying a step pulse to +100 mV from the holding potential of −90 mV to CHO-K1 cells expressing hBKα channels, and the current amplitude in the presence of a test compound (30 μM) was expressed as percent of the drug-free control. The values represent an average of data obtained from at least eight separate measurements. The results for NS1619 are included for comparison.

### 3.1. Dehydroabietic acid case

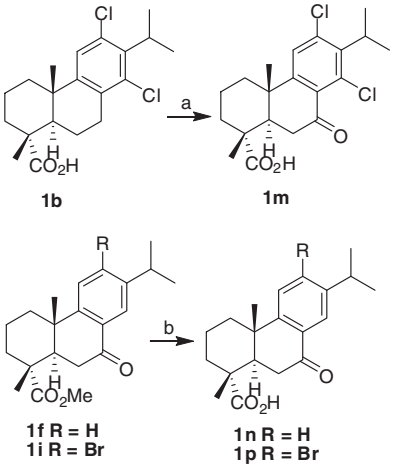
In the present work we mainly focused on the effect of simple alkyl modifications at the oxime to probe the effect of oximic substitution on the BK channel-opening activity (Table 1). In our preliminary study, we found that introduction of a phenyl-substituted carbon chain on the oxime oxygen atom had little influence or




**Scheme 6.** Reagents and conditions: (a) NBS, Mont. K10, $CH_3CN$, rt, 69% (**1g**/**1h** = 3.1:1); (b) $CrO_3$, AcOH/$Ac_2O$, 83%; (c) $NH_2OH{\cdot}HCl$, EtOH, Py, reflux, 97%; (d) KOBu$^t$, DMSO, rt, 52%; (e) RBr, NaH, DMF, 0 °C to rt, 73% (**5u**) and 70% (**5v**); (f) KOH, 18-crown-6, MeOH, reflux, 90% (**3u**) and 72% (**3v**).




**Scheme 7.** Reagents and conditions: (a) $Cl_2$, $FeCl_3/SiO_2$, DDQ/$SiO_2$, $CCl_4$, 35%; (b) $TMSCHN_2$ (2 M, in $Et_2O$), MeOH–toluene, rt, 94%; (c) $CrO_3$, AcOH/$Ac_2O$, 82%; (d) $NH_2OH{\cdot}HCl$, EtOH, Py, reflux, 84%; (e) RBr, NaH, DMF, 0 °C to rt, 99–100%; (f) KOH, 18-crown-6, MeOH, microwave irridiation, 145 °C, 56–86%.

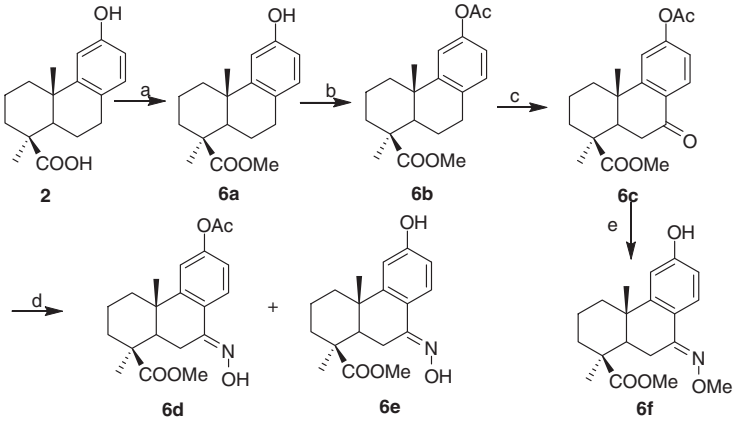



**Scheme 8.** Reagents and conditions: (a) $CrO_3$, AcOH/$Ac_2O$, 36%; (b) $KOBu^t$, DMSO, rt, 58% (**1n**) and 15% (**1p**).

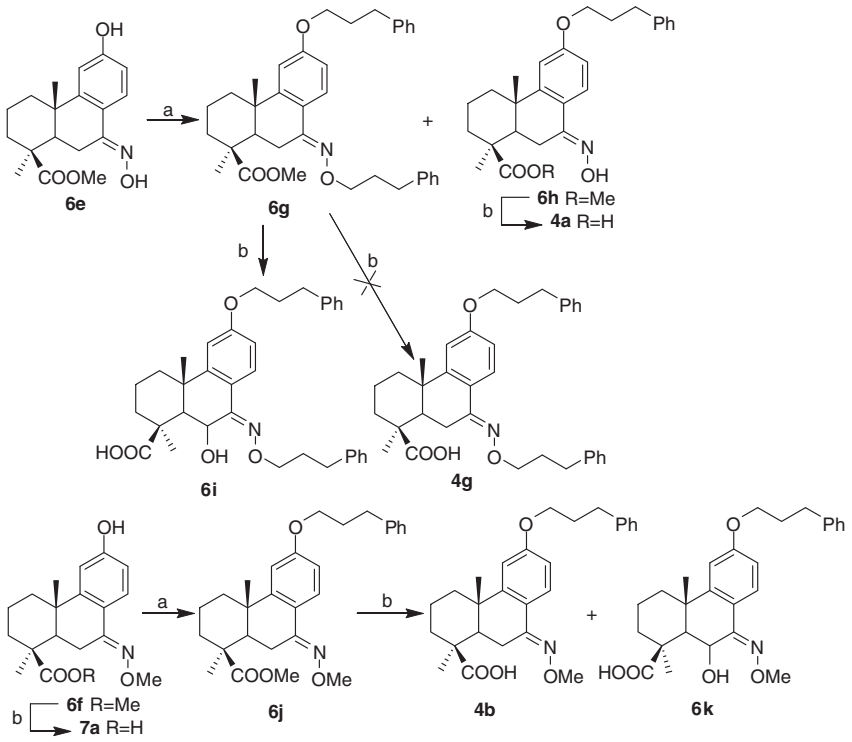
decreased the BK channel-opening activity as compared with the O-unsubstituted oxime (**3a**).

For the diCl-DHAA series of compounds **3a**–**m**, when R changed from methyl (**3b**), ethyl (**3c**), to propyl (**3d** and **3e**), the activity decreased. In the case of the propyl substituent, the straight-chain derivative (**3d**) showed slightly higher activity than the branched side chain derivative (**3e**). A long substituent chain decreased the activity (e.g., compound **3l** showed almost no BK-opening activity). Introduction of a small unsaturated substituent, such as allyl, greatly increased the potency (**3f** vs **3d**). However, further appending two terminal methyl groups dramatically decreased the activity, which became even lower than that of the corresponding saturated derivative (**3h** vs **3i**). The cyclopropanemethylene derivative (**3j**) also showed potent activity. However, introduction of a large ring dramatically decreased the activity (compound **3k**). Compounds **3b**, **3c**, **3f**, and **3g** showed potency comparable to or higher than that of NS1619.

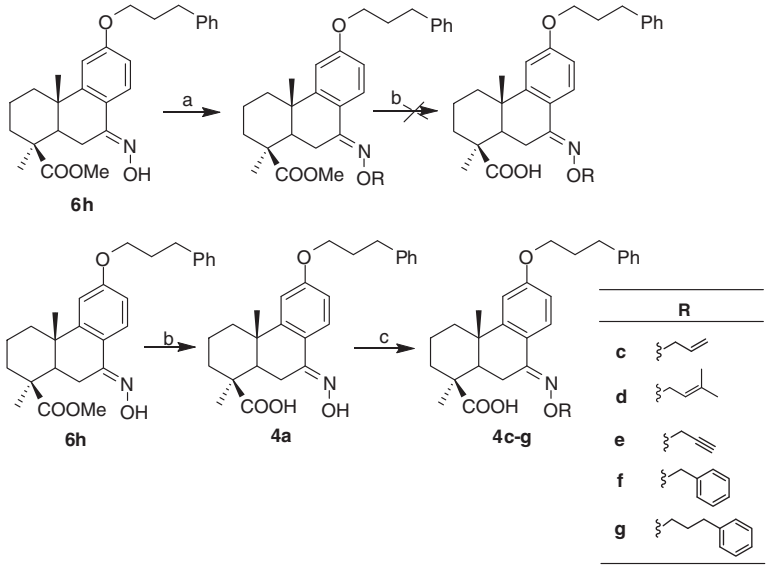
For the non-chlorinated DHAA series of compounds (Table 1), the influence of the substituents on the oxime chain upon the activity showed a very similar trend to that in the diCl-DHAA series, though the range of activity is rather low. The oxime **3n** (ion current = 120.7 ± 9.6% of control at 30 μM) was found to be a moderate BK channel opener, with slightly lower potency than that of the corresponding diCl-DHAA oxime **3a** (137 ± 3.6%). Introduction of a small saturated substituent such as methyl (**3o**, 152.8 ± 8.3%) or small unsaturated substituents (**3p**, 182.5 ± 8.3%; **3q**, 142.1 ± 14.1%) increased the potency. On the other hand, introduction of a phenyl-substituted carbon chain, such as a benzyl group, had little influence (**3r**) as compared with the O-unsubstituted oxime **3n**. It is noteworthy that additional insertion of two methylene spacers (**3s**) increased the activity. Moreover, the activities of




**Scheme 9.** Reagents and conditions: (a) $TMSCHN_2$, MeOH, toluene, rt, 100%; (b) $CH_3COONa$, $Ac_2O$, reflux, 90%; (c) $CrO_3$, AcOH/$Ac_2O$, rt, 85%; (d) $NH_2OH{\cdot}HCl$, EtOH, pyridine, reflux, 3 h; (e) $NH_2OMe{\cdot}HCl$, EtOH, pyridine, reflux, overnight (17 h), 83%.




**Scheme 10.** Reagents and conditions: (a) 1-bromo-3-phenylpropane, $Cs_2CO_3$, DMF; (b) KOBu$^t$, DMSO, 60 °C.




**Scheme 11.** Reagents and conditions: (a) RBr, NaH, DMF, 0 °C to rt; (b) KOBu$^t$, DMSO, 60 °C; (c) RBr, KOH, NaI (cat.), EtOH, reflux, 61–98% conversion yield.

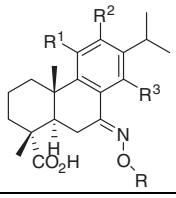
all the DHAA series were lower than those of the corresponding diCl-DHAA derivatives, indicating the importance of the chloride functionality in ring C for the activity.

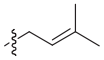
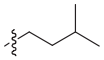
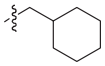
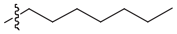
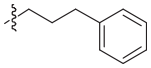
In the 12-Br-DHAA series (Table 1), the oxime itself **3t** (ion current = 162.3 ± 11.7% of control at 30 μM) was found to be a potent BK opener, with much higher potency than that of the corresponding diCl-DHAA oxime **3a** (137 ± 3.6%). Introduction of a small saturated substituent such as methyl (**3u**, 216.5 ± 27.2%) or a small unsaturated allyl substituent (**3v**, 237.2 ± 23.3%) greatly increased the potency.

In the triCl-DHAA series (Table 1), the oxime **3w** (ion current = 229 ± 15.8% of control at 30 μM) was found to be the most potent BK opener among the four O-unsubstituted oxime derivatives (**3a**, **3n**, **3t**, and **3w**). Introduction of a small saturated substituent such as methyl (**3x**, 235.3 ± 23.4%) marginally increased the potency. However, in contrast to the other three series of compounds, introduction of a small unsaturated substituent such as an allyl group (**3y**, 183.5 ± 7.3%) decreased the potency compared with the O-unsubstituted oxime **3w**.

As mentioned above, we also synthesized the ketone derivatives to confirm the importance of the oximic group for BK channel-opening activity. Interestingly, the 12-Br-DHAA ketone derivative showed marginally higher activity than the corresponding O-unsubstituted oxime (**1p** vs **3t**), while the DHAA ketone derivative

**Table 1**
Structure and BKα-opening properties of dehydroabietate derivatives




| Compound | $R^1$ | $R^2$ | $R^3$ | R | Ionic current in the presence of test compound (30 μM) as % of control current ($n$ = 8) |
|---|---|---|---|---|---|
| Buffer | — | — | — | — | 100.4 ± 2.3 |
| NS1619 | — | — | — | — | 280.7 ± 15.6 |
| **1m** | — | — | — | — | 123.5 ± 4.0 |
| **3a** | H | Cl | Cl | H | 137.0 ± 3.6 |
| **3b** | H | Cl | Cl | $CH_3$ | 213.1 ± 9.4 |
| **3c** | H | Cl | Cl |  | 211.8 ± 3.9 |
| **3d** | H | Cl | Cl |  | 191.7 ± 13.8 |
| **3e** | H | Cl | Cl |  | 183.5 ± 12.2 |
| **3f** | H | Cl | Cl |  | 297.4 ± 17.2 |
| **3g** | H | Cl | Cl |  | 260.8 ± 21.6 |
| **3h** | H | Cl | Cl |  | 125.6 ± 8.4 |
| **3i** | H | Cl | Cl |  | 144.8 ± 10.7 |
| **3j** | H | Cl | Cl |  | 180.8 ± 7.9 |
| **3k** | H | Cl | Cl |  | 128.6 ± 7.8 |
| **3l** | H | Cl | Cl |  | 111.2 ± 7.1 |
| **3m** | H | Cl | Cl | $CH_2Ph$ | 151.1 ± 15.1 |
| **1n** | — | — | — | — | 100.3 ± 3.7 |
| **3n** | H | H | H | H | 120.7 ± 9.6 |
| **3o** | H | H | H | $CH_3$ | 152.8 ± 8.3 |
| **3p** | H | H | H |  | 182.5 ± 8.3 |
| **3q** | H | H | H |  | 142.1 ± 14.1 |
| **3r** | H | H | H | $CH_2Ph$ | 123.0 ± 7.7 |
| **3s** | H | H | H |  | 143.2 ± 6.2 |
| **1p** | — | — | — | — | 166.2 ± 11.3 |
| **3t** | H | Br | H | H | 162.3 ± 11.7 |
| **3u** | H | Br | H | $CH_3$ | 216.5 ± 27.2 |
| **3v** | H | Br | H |  | 237.2 ± 23.3 |
| **3w** | Cl | Cl | Cl | H | 229.0 ± 15.8 |
| **3x** | Cl | Cl | Cl | $CH_3$ | 235.3 ± 23.4 |
| **3y** | Cl | Cl | Cl |  | 183.5 ± 7.3 |

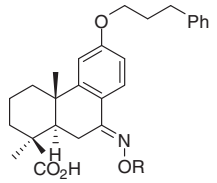
(**1n**) showed no activity. The diCl-DHAA ketone derivative (**1m**) showed weak activity.

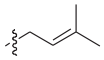
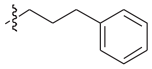
### 3.2. Podocarpic acid case

Our previous study showed that the podocarpic acid structure represents a new scaffold for BK channel openers.[25] A preliminary SAR study of podocarpic acid derivatives showed that podocarpic acid itself has BK channel-opening activity, and introduction of a 12-alkoxy substituent, in particular, the phenylpropyl group dramatically increased BK channel-opening activity. Thus, we kept this preponderant functionality at the 12-oxy position and studied the effect of oximation and the substituent effect at the oxime on BK channel-opening activity (Table 2).

In the podocarpate series of compounds, the oxime itself **4a** (ion current = 134.1 ± 13% of control at 30 μM) was found to be a moderately active BK opener. Introduction of a small saturated substituent such as methyl (**4b**, 151.1 ± 14%) or small unsaturated substituents (**4c**, 159.9 ± 4.4%; **4e**, 166.2 ± 9%), as well as a phenyl-substituted carbon chain (**4f**, 151.5 ± 14.3%), increased the potency. However, 3-methyl-2-butenyl (**4d**) or phenylpropyl (**4g**) substitutions had little effect compared with **4a**. It is interesting that compound **7a** showed almost no BK channel-opening activity; this suggests the importance of the *O*-phenylpropyl group in ring C for the activity. And hydroxylation of the 6-position decreased the potency compared with the corresponding carboxylic acids (**6i** vs **4g**; **6k** vs **4b**).

**Table 2**
Structure and BKα-opening properties of podocarpate derivatives




| Compound | R | Ionic current in the presence of test compound (30 μM) as % of control current ($n$ = 8) |
|---|---|---|
| Buffer | — | 100.4 ± 2.3 |
| NS1619 | — | 280.7 ± 15.6 |
| **7a** | — | 103.0 ± 3.1 |
| **4a** | H | 134.1 ± 13 |
| **4b** | $CH_3$ | 151.1 ± 14 |
| **4c** |  | 159.9 ± 4.4 |
| **4d** |  | 137.9 ± 4.7 |
| **4e** |  | 166.2 ± 9 |
| **4f** | $CH_2Ph$ | 151.5 ± 14.3 |
| **4g** |  | 133.6 ± 9.3 |
| **6i** | — | 107.0 ± 3.1 |
| **6k** | — | 124.6 ± 10.6 |

## 4. Conclusion

Our results indicate that the oxime structure is a suitable scaffold for designing novel potent BK openers. Detailed SAR analysis showed that oximation was particularly effective in the case of dehydroabietic acid derivatives. Unsubstituted, dichloro, trichloro and monobromo derivatives of the C-ring of dehydroabietic acid showed similar substituent effects with respect to the oxime O-substituent, whereas oximation had relatively little effect in the case of podocarpic acid derivatives. Some of the oxime derivatives showed more potent BK channel activities than did the standard compound, NS1619. The present studies provide a new structural basis for development of efficient BK channel openers with clinical potential to control pathologically uncontrolled cell excitation.

## 5. Experimental section

### 5.1. General procedures

Commercial reagents were used without further purification, unless otherwise mentioned. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$, DMSO-$d_6$ or Acetone-$d_6$. Chemical shifts are reported in parts per million (ppm) and coupling constants ($J$) are reported in hertz (Hz). Chemical shifts in $CDCl_3$ were reported on a scale relative to $CHCl_3$ (7.26 ppm) for $^1$H NMR, and to $CDCl_3$ (77.23 ppm) for $^{13}$C NMR, as internal references. The center lines of the multiplets of DMSO-$d_6$ or acetone-$d_6$ were defined as 2.50 and 2.05 ppm respectively, and used as internal references for $^1$H NMR spectra. High-resolution mass spectra (HR-MS) were recorded on a Bruker Daltonics MicrOTOF05 in the electro-spray ionization (ESI)-time-of-flight (TOF) detection mode. Elemental analyses were carried out on a Yanaco CHN CORDER spectrometer at the Analysis Center of the Graduate School of Pharmaceutical Sciences, the University of Tokyo. Flash column chromatography was carried out with silica gel (Kanto Chemical 60 N, particle size 40–50 μm). Melting points were measured on a Yanaco hot-stage microscope and are uncorrected. Yields represent those of isolated pure materials. Microwave heating was carried out on a Biotage Initiator system (300W).

#### 5.1.1. diCl-DHAA series

**5.1.1.1. 12,14-Dichlorodehydroabietic acid (1b).** To a suspension of dehydroabietic acid **4a** (2.0 g, 6.66 mmol), 2% w/w $FeCl_3$ on $SiO_2$ (1 g), and 1% w/w DDQ on $SiO_2$ (0.1 g) in 25 mL $CCl_4$ was added a solution of 2.0 M $Cl_2$ in 40 mL $CCl_4$ at 0 °C. The reaction mixture was vigorously stirred at rt for 1.5 h. The reaction was quenched with saturated $Na_2SO_3$, and the whole was extracted with $CHCl_3$ three times. The combined organic layer was washed with brine, and dried over $Na_2SO_4$. The residue was recrystallized from $n$-hexane to afford **1b** (962 mg, yield 39%) as a colorless solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.15 (br s, 1H), 3.91 (br s, 1H), 2.94 (dd of ABX system, $J$ = 18.2, 6.2 Hz, 1H), 2.79–2.70 (m, 1H), 2.24 (d, $J$ = 12.6 Hz, 1H), 2.13 (dd of ABX system, $J$ = 12.6, 1.9 Hz, 1H), 1.86–1.61 (m, 7H), 1.39 (d, $J$ = 7.2 Hz, 6H),1.28 (s, 3H), 1.20 (s, 3H).

**5.1.1.2. 12,14-Dichlorodehydroabietic acid methyl ester (1c).** To a solution of **1b** (962 mg, 2.605 mmol) in MeOH (4.4 mL) and PhMe (8.8 mL) was added dropwise 2.0 M $TMSCHN_2$ in $Et_2O$ (1.7 mL, 3.4 mmol) at rt over 5 min, and the whole was stirred at rt for 30 min. Excess $TMSCHN_2$ was quenched with AcOH, then the reaction mixture was evaporated in vacuo, and the residue was purified by flash chromatography ($n$-hexane only to $n$-hexane/AcOEt = 10:1) to afford **1c** (900 mg, yield 90%) as a colorless solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.16 (br s, 1H), 3.91 (br s, 1H), 3.67 (s, 3H), 2.92 (dd of ABX system, $J$ = 18.2, 6.2 Hz, 1H), 2.76–2.66 (m, 1H), 2.23 (d, $J$ = 11.4 Hz, 1H), 2.12 (dd of ABX system, $J$ = 12.8, 2.1 Hz, 1H), 1.83–1.61 (m, 7H), 1.39 (d, $J$ = 7.2 Hz, 6H), 1.26 (s, 3H), 1.19 (s, 3H).

**5.1.1.3. 13-Isopropyl-12,14-dichloro-7-oxopodocarpe-8,11,13-triene-15-carboxylic acid methyl ester (1d).** To a solution of $CrO_3$ (287 mg, 2.867 mmol) in $Ac_2O$ (9 mL) and AcOH (4 mL) was added dropwise a suspension of the methyl ester **1c** (999 mg, 2.606 mmol) in AcOH (15 mL) at 0 °C over 10 min. The reaction mixture was stirred at 50 °C for 9 h, cooled, and poured into ice-water (40 mL) and then the whole was extracted with $CHCl_3$ 3 times. The combined organic layer was washed with water, sat. $NaHCO_3$, and brine, and dried over $Na_2SO_4$. The crude mixture was purified by flash chromatography ($n$-hexane/AcOEt = 12:1) to afford **1d** (600 mg, yield 58%) as a colorless solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.23 (br s, 1H), 4.09 (br s, 1H), 3.66 (s, 3H), 2.65 (m, 2H), 2.50 (dd of ABX system, $J$ = 16.9, 5.2 Hz, 1H), 2.20 (d, $J$ = 12.4 Hz, 1H), 1.80–1.76 (m, 5H), 1.40 (d, $J$ = 7.2 Hz, 6H), 1.32 (s, 3H), 1.19 (s, 3H).

**5.1.1.4. 12,14-Dichloro-13-isopropyl-7-hydroxyiminepodocarpe-8,11,13-triene-15-carboxylic acid methyl ester (5a).** A mixture of the methyl ester **1d** (430 mg, 1.08 mmol), pyridine (0.13 mL), and $NH_2OH$·HCl (120 mg, 1.727 mmol in EtOH (4.4 mL) was stirred at 100 °C for 3 h, then cooled, and evaporated in vacuo. The residue was purified by flash chromatography ($n$-hexane/AcOEt = 5:1) to afford **4e** (386 mg, yield 87%) as a colorless solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 10.02 (br s, 1H), 7.15 (br s, 1H), 4.09 (br s, 1H), 3.66 (s, 3H), 3.08 (dd of ABX system, $J$ = 18.6, 13.1 Hz, 1H), 2.39 (dd of ABX system, $J$ = 18.6, 6.4 Hz, 1H), 2.16 (dd, $J$ = 13.0, 6.4 Hz, 2H), 1.74–1.56 (m, 5H), 1.44 (d, $J$ = 6.0 Hz, 6H),1.36 (s, 3H), 1.04 (s, 3H).

**5.1.1.5. 12,14-Dichloro-13-isopropyl-7-methoxyiminepodocarpe-8,11,13-triene-15-carboxylic acid methyl ester (5b).** A mixture of the methyl ester **1d** (29 mg, 0.073 mmol), pyridine (10 μL), and $NH_2OMe$·HCl (10 mg, 0.120 mmol) in EtOH (1 mL) was stirred at 100 °C for 3 h, then cooled, and evaporated in vacuo. The residue

was purified by flash chromatography (*n*-hexane/AcOEt = 8:1) to afford **5b** (31 mg, yield 100%) as a colorless solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.13 (br s, 1H), 4.07 (br s, 1H), 4.03 (s, 3H), 3.64 (s, 3H), 2.98 (dd of ABX system, $J$ = 18.5, 13.0 Hz, 1H), 2.29 (dd of ABX system, $J$ = 18.5, 6.4 Hz, 1H), 2.12 (dd, $J$ = 13.1, 6.4 Hz, 2H), 1.79–1.52 (m, 5H), 1.41 (d, $J$ = 5.6 Hz, 3H), 1.39 (d, $J$ = 6.4 Hz, 3H), 1.36 (s, 3H), 1.06 (s, 3H).

### 5.2. General procedure for preparation of compounds 5f–g, 5m

A mixture of the methyl ester **5a** (41 mg, 0.1 mmol), the corresponding alkyl or aryl bromide (0.15 mmol), cat. $Bu^n{}_4N^+Br^-$ (TBAB) (3 mg) and 1 N KOH (0.15 mL) in dichloromethane (DCM) (1 mL) was stirred at 40 °C overnight, then cooled, and diluted with $H_2O$. The whole was extracted with AcOEt. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and evaporated in vacuo. The residue was purified by flash chromatography using *n*-hexane/ethyl acetate as the eluent to afford **5f**–**g**, **5m**.

#### 5.2.1. (*E*,1*R*,4a*S*,10a*R*)-Methyl 9-(allyloxy)imino-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5f)

Colorless solid, yield 62%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.13 (br s, 1H), 6.13–6.04 (m, 1H), 5.33 (m, 2H), 4.72 (m, 2H), 4.08 (br s, 1H), 3.65 (s, 3H), 3.01 (dd of ABX system, $J$ = 18.6, 13.0 Hz, 1H), 2.32 (dd of ABX system, $J$ = 18.6, 6.4 Hz, 1H), 2.15 (d, $J$ = 8.4 Hz, 1H), 2.11 (dd of ABX system, $J$ = 13.0, 6.4 Hz, 1H), 1.77–1.65 (m, 4H), 1.63–1.52 (m, 1H), 1.41 (d, $J$ = 6.7 Hz, 6H), 1.37 (s, 3H), 1.07 (s, 3H).

#### 5.2.2. (*E*,1*R*,4a*S*,10a*R*)-Methyl 9-((prop-2-ynyloxy)imino)-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5g)

Yellow oil, yield 79%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.13 (br s, 1H), 4.81 (m, 2H),4.09 (br s, 1H), 3.65 (s, 3H), 3.00 (dd of ABX system, $J$ = 18.6, 13.0 Hz, 1H), 2.48 (t, $J$ = 2.4 Hz, 1H), 2.35 (dd of ABX system, $J$ = 18.6, 6.4 Hz, 1H), 2.16–2.09 (m, 2H), 1.77–1.56 (m, 5H), 1.41 (d, $J$ = 6.8 Hz, 6H), 1.37 (s, 3H), 1.07 (s, 3H).

#### 5.2.3. (*E*,1*R*,4a*S*,10a*R*)-Methyl 9-(benzyloxy)imino-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5m)

Yellow oil, yield 85%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.45–7.35 (m, 5H), 7.13 (br s, 1H), 5.29 (d of AB system, $J$ = 12.6 Hz, 1H), 5.25 (d of AB system, $J$ = 12.6 Hz, 1H), 4.06 (br s, 1H), 3.65 (s, 3H), 3.05 (dd of ABX system, $J$ = 18.6, 13.0 Hz, 1H), 2.34 (dd of ABX system, $J$ = 18.6, 6.4 Hz, 1H), 2.16–2.09 (m, 2H), 1.81–1.63 (m, 4H), 1.62–1.53 (m, 1H), 1.41 (d, $J$ = 6.2 Hz, 6H), 1.37 (s, 3H), 1.05 (s, 3H).

### 5.3. General procedure for preparation of compounds 3a–b, 3f–g, 3m (Method A)

A mixture of the methyl ester **5a**–**b**, **5f**–**g**, **5m** (0.1 mmol), KOH (56 mg, 1 mmol) and 18-crown ether-6 (132 mg, 0.5 mmol) in MeOH (2 mL) was stirred at 80 °C for 24 h, then cooled, and evaporated in vacuo. The residue was diluted with water (10 mL), acidified with 2 N HCl, and extracted with AcOEt. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and evaporated in vacuo. The residue was purified by flash chromatography using *n*-hexane/ethyl acetate as the eluent to afford **3a**–**b**, **3f**–**g**, **3m**.

#### 5.3.1. (*E*,1*R*,4a*S*,10a*R*)-6,8-Dichloro-1,2,3,4,4a,9,10,10a-octahydro-9-(hydroxyimino)-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3a)

Colorless solid, yield 88%. Mp 284–286 °C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.14 (br s, 1H), 4.03 (br s, 1H), 3.11 (dd of ABX system, $J$ = 18.8, 13.0 Hz, 1H), 2.53 (dd of ABX system, $J$ = 18.8, 6.4 Hz, 1H), 2.15 (dd, $J$ = 12.9, 6.5 Hz, 2H), 1.80–1.71 (m, 4H), 1.62–1.53 (m, 1H), 1.40 (d, $J$ = 6.2 Hz, 6H),1.38 (s, 3H), 1.05 (s, 3H). HR-MS: calcd for $C_{20}H_{25}{}^{35}Cl_2NO_3$ ($[M+H]^+$), 398.1289; found, 398.1333.

Anal. Calcd for $C_{20}H_{25}Cl_2NO_3{\cdot}1/2H_2O$: C, 58.97; H, 6.43; N, 3.44. Found: C, 58.81; H, 6.19; N, 3.21.

#### 5.3.2. (*E*,1*R*,4a*S*,10a*R*)-6,8-Dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-9-methoxyimino-1,4a-dimethylphenanthrene-1-carboxylic acid (3b)

Colorless oil, yield 79%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.12 (br s, 1H), 4.09 (br s, 1H),4.04 (s, 3H), 3.00 (dd of ABX system, $J$ = 18.6, 13.1 Hz, 1H), 2.42 (dd of ABX system, $J$ = 18.6, 6.4 Hz, 1H), 2.14 (d, $J$ = 12.2, Hz, 1H), 2.08 (dd of ABX system, $J$ = 13.1, 6.4 Hz, 1H), 1.79–1.72 (m, 4H), 1.69–1.59 (m, 1H), 1.41 (d, $J$ = 6.4 Hz, 1H), 1.36 (s, 3H), 1.07 (s, 3H). HR-MS: calcd for $C_{21}H_{27}{}^{35}Cl_2NO_3$ ($[M+Na]^+$), 434.1266; found, 434.1270.

Anal. Calcd for $C_{21}H_{27}Cl_2NO_3{\cdot}2/5H_2O$: C, 60.12; H, 6.68; N, 3.34. Found: C, 60.45; H, 6.84; N, 2.93.

#### 5.3.3. (*E*,1*R*,4a*S*,10a*R*)-9-(Allyloxy)imino-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3f)

Colorless oil, yield 85%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.15 (br s, 1H), 6.14–6.04 (m, 1H), 5.34 (dd, $J$ = 18.7, 1.6 Hz, 1H), 5.23 (dd, $J$ = 10.4,1.6 Hz, 1H), 4.74 (m, 2H), 4.09 (br s, 1H), 3.03 (dd of ABX system, $J$ = 18.6,13.0 Hz, 1H), 2.46 (dd of ABX system, $J$ = 18.6, 6.4 Hz, 1H), 2.15 (d, $J$ = 12.1 Hz, 1H), 2.09 (dd of ABX system, $J$ = 13.0, 6.4 Hz, 1H), 1.79–1.69 (m, 4H), 1.63–1.53 (m, 1H), 1.40 (d, $J$ = 6.9 Hz, 6H), 1.37 (s, 3H), 1.07 (s, 3H). HR-MS: calcd for $C_{23}H_{29}{}^{35}Cl_2NO_3$ ($[M+Na]^+$), 460.1422; found, 460.1388.

Anal. Calcd for $C_{23}H_{29}Cl_2NO_3{\cdot}1/4H_2O$: C, 62.37; H, 6.71; N, 3.16. Found: C, 62.44; H, 6.50; N, 2.97.

#### 5.3.4. (*E*,1*R*,4a*S*,10a*R*)-9-((Prop-2-ynyloxy)imino)-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3g)

Yellow oil, yield 70%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.13 (br s, 1H), 4.82 (m, 2H),4.09 (br s, 1H), 3.03 (dd of ABX system, $J$ = 18.6, 13.0 Hz, 1H), 2.49 (dd of ABX system, $J$ = 18.6, 6.4 Hz, 1H), 2.48 (t, $J$ = 2.4 Hz, 1H), 2.15 (d, $J$ = 11.9 Hz, 1H), 2.10 (dd of ABX system, $J$ = 13.0, 6.4 Hz, 1H), 1.80–1.70 (m, 4H), 1.65–1.53 (m, 1H), 1.41 (d, $J$ = 5.8 Hz, 6H), 1.37 (s, 3H), 1.08 (s, 3H). HR-MS: calcd for $C_{23}H_{27}{}^{35}Cl_2NO_3$ ($[M+Na]^+$), 458.1266; found, 458.1242.

Anal. Calcd for $C_{23}H_{27}Cl_2NO_3$: C, 63.31; H, 6.24; N, 3.21. Found: C, 63.26; H, 6.18; N, 2.97.

#### 5.3.5. (*E*,1*R*,4a*S*,10a*R*)-9-(Benzyloxy)imino-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3m)

Yellow oil, yield 48%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.44–7.42 (m, 2H), 7.38–7.30 (m, 3H), 7.11 (br s, 1H), 5.28 (d of AB system, $J$ = 12.6 Hz, 1H), 5.24 (d of AB system, $J$ = 12.6 Hz, 1H), 4.10 (br s, 1H), 3.06 (dd of ABX system, $J$ = 18.6, 13.0 Hz, 1H), 2.46 (dd of ABX system, $J$ = 18.6, 6.4 Hz, 1H), 2.14 (d, $J$ = 12.1 Hz, 1H), 2.09 (dd of ABX system, $J$ = 13.0, 6.4 Hz, 1H), 1.79–1.68 (m, 4H), 1.62–1.52 (m, 1H), 1.39 (d, $J$ = 6.2 Hz, 6H), 1.36 (s, 3H), 1.04 (s, 3H). HR-MS: calcd for $C_{27}H_{31}{}^{35}Cl_2NO_3$ ($[M+Na]^+$), 510.1579; found, 510.1552.

### 5.4. General procedure for preparation of compounds 5c–e, 5h–l (Method B)

To a solution of compound **5a** (0.1 mmol) in 2 mL DMF was added NaH (6 mg, 0.15 mmol, 60% in mineral oil) at about 0 °C, in a flask fitted with a $CaCl_2$ tube. The mixture was stirred at 0 °C for 30 min, the corresponding bromide (0.15 mmol) was added, and the solution was gradually warmed to rt, then stirred overnight. The reaction was quenched with saturated aqueous $NH_4Cl$, and the whole was extracted with AcOEt. The combined organic layer was washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and evaporated in vacuo. The residue was purified by flash chromatography using *n*-hexane/ethyl acetate as the eluent to afford **5c–e**, **5h–l**.

#### 5.4.1. (*E*,1*R*,4a*S*,10a*R*)-Methyl 6,8-dichloro-9-ethoxyimino-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5c)

Yellow oil, yield 56%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.12 (br s, 1H), 4.25 (m, 2H), 4.09 (br s, 1H), 3.64 (s, 3H), 2.98 (dd of ABX system, $J$ = 18.5, 13.0 Hz, 1H), 2.28 (dd of ABX system, $J$ = 18.5, 6.4 Hz, 1H), 2.12 (m, 2H), 1.85–1.58 (m, 5H), 1.41 (d, $J$ = 7.2 Hz, 6H), 1.36 (s, 3H), 1.34 (t, $J$ = 7.2 Hz, 3H), 1.05 (s, 3H).

#### 5.4.2. (*E*,1*R*,4a*S*,10a*R*)-Methyl 6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethyl-9-propoxyiminophenanthrene-1-carboxylate (5d)

Light yellow oil, yield 75%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.12 (br s, 1H), 4.22–4.07 (m, 3H), 3.65 (s, 3H), 3.00 (dd of ABX system, $J$ = 18.4, 13.0 Hz, 1H), 2.28 (dd of ABX system, $J$ = 18.4, 6.4 Hz, 1H), 2.15–2.08 (m, 2H), 1.80–1.66 (m, 6H), 1.63–1.56 (m, 1H), 1.41 (d, $J$ = 5.8 Hz, 6H),1.37 (s, 3H), 1.06 (s, 3H), 0.96 (t, $J$ = 7.4 Hz, 3H).

#### 5.4.3. (*E*,1*R*,4a*S*,10a*R*)-Methyl 6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-9-isopropoxyimino-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5e)

Light yellow oil, yield 61%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.12 (br s, 1H), 4.48–4.41 (m, 1H), 4.10 (br s, 1H), 3.65 (s, 3H), 2.97 (dd of ABX system, $J$ = 18.4, 13.0 Hz, 1H), 2.25 (dd of ABX system, $J$ = 18.4, 6.4 Hz, 1H), 2.16–2.08 (m, 2H), 1.76–1.65 (m, 4H), 1.63–1.56 (m, 1H), 1.41 (d, $J$ = 7.6 Hz, 6H), 1.37 (s, 3H), 1.35 (d, $J$ = 6.4 Hz, 3H), 1.29 (d, $J$ = 6.4 Hz, 3H), 1.06 (s, 3H).

#### 5.4.4. (*E*,1*R*,4a*S*,10a*R*)-Methyl 9-((3-methylbut-2-enyloxy)imino)-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5h)

Light yellow solid, yield 83%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.12 (br s, 1H), 5.50 (m, 1H), 4.76–4.66 (m, 2H), 4.10 (br s, 1H), 3.64 (s, 3H), 2.98 (dd of ABX system, $J$ = 18.5, 13.0 Hz, 1H), 2.30 (dd of ABX system, $J$ = 18.5, 6.4 Hz, 1H), 2.15–2.08 (m, 2H), 1.78 (s, 3H), 1.73 (s, 3H), 1.69 (m, 4H), 1.61 (m, 1H), 1.41 (d, $J$ = 6.8 Hz, 6H), 1.36 (s, 3H), 1.06 (s, 3H).

#### 5.4.5. (*E*,1*R*,4a*S*,10a*R*)-Methyl 9-(isopentyloxy)imino-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5i)

Light yellow oil, yield 74%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.12 (br s, 1H), 4.25 (m, 2H), 4.10 (m, 1H), 3.65 (s, 3H), 2.99 (dd of ABX system, $J$ = 18.5, 13.0 Hz, 1H), 2.32–2.23 (m, 1H), 2.15–2.04 (m, 2H), 1.78–1.55 (m, 8H), 1.41 (d, $J$ = 6.0 Hz, 6H), 1.36 (s, 3H), 1.06 (s, 3H), 0.95 (d, $J$ = 6.5 Hz, 3H), 0.94 (d, $J$ = 6.5 Hz, 3H). HR-MS: calcd for $C_{25}H_{35}{}^{35}Cl_2NO_3$ ([M+Na]$^+$), 490.1892; found, 490.1891.

#### 5.4.6. (*E*,1*R*,4a*S*,10a*R*)-Methyl 9-(cyclopropylmethoxy)imino-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5j)

Colorless oil, yield 85%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.13 (br s, 1H), 4.07 (m, 3H), 3.65 (s, 3H), 3.02 (dd of ABX system, $J$ = 18.5, 13.0 Hz, 1H), 2.32 (dd of ABX system, $J$ = 18.5, 6.4 Hz, 1H), 2.16–2.10 (m, 2H), 1.74–1.70 (m, 4H), 1.61 (m, 1H), 1.41 (d, $J$ = 6.2 Hz, 6H), 1.37 (s, 3H), 1.25 (m, 1H), 1.07 (s, 3H), 0.58–0.54 (m, 2H), 0.37–0.34 (m, 1H), 0.31–0.26 (m, 1H). HR-MS: calcd for $C_{24}H_{31}{}^{35}Cl_2NO_3$ ([M+Na]$^+$), 474.1579; found, 474.1576.

#### 5.4.7. (*E*,1*R*,4a*S*,10a*R*)-Methyl 9-(cyclohexylmethoxy)imino-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5k)

Light yellow oil, yield 73%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.12 (br s, 1H), 4.04 (m, 2H), 3.94 (m, 1H), 3.65 (s, 3H), 3.01 (dd of ABX system, $J$ = 18.4, 13.0 Hz, 1H), 2.27 (m, 1H), 2.15–2.08 (m, 2H), 1.85–1.56 (m, 10H), 1.41 (d, $J$ = 6.5 Hz, 6H), 1.37 (s, 3H), 1.27–1.16 (m, 4H), 1.06 (s, 3H), 1.01–0.92 (m, 2H).

#### 5.4.8. (*E*,1*R*,4a*S*,10a*R*)-Methyl 9-(heptyloxy)imino-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5l)

Light yellow oil, yield 86%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.12 (br s, 1H), 4.25–4.08 (m, 3H), 3.65 (s, 3H), 2.99 (dd of ABX system, $J$ = 18.5, 13.0 Hz, 1H), 2.27 (dd of ABX system, $J$ = 18.5, 6.5 Hz, 1H), 2.15–2.08 (m, 2H), 1.76–1.70 (m, 6H), 1.66–1.56 (m, 1H), 1.41 (d, $J$ = 6.5 Hz, 6H),1.36 (s, 3H), 1.38–1.23 (m, 8H), 1.06 (s, 3H), 0.88 (t, $J$ = 6.6 Hz, 3H).

### 5.5. General procedure for preparation of compounds 3d–e, 3i–l (Method C)

Compounds **5d–e**, **5i–l** (0.1 mmol) was treated with KOBu$^t$ (1.5 mmol) in DMSO (1.5 mL) at room temperature for about 40 min. Then the reaction mixture was poured into ice-water, acidified with 2 N HCl and extracted with AcOEt. The combined organic layer was washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and evaporated in vacuo. The residue was purified by flash chromatography using *n*-hexane/ethyl acetate as the eluent to afford **3d–e**, **3i–l**.

#### 5.5.1. (*E*,1*R*,4a*S*,10a*R*)-6,8-Dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethyl-9-propoxyiminophenanthrene-1-carboxylic acid (3d)

Light yellow oil, yield 45%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.11 (br s, 1H), 4.21–4.09 (m, 3H), 3.02 (dd of ABX system, $J$ = 18.5, 13.0 Hz, 1H), 2.42 (dd of ABX system, $J$ = 18.5, 6.4 Hz, 1H), 2.14 (d, $J$ = 12.0 Hz, 1H), 2.09 (dd of ABX system, $J$ = 13.0, 6.4 Hz, 1H), 1.81–1.69 (m, 6H), 1.63–1.60 (m, 1H), 1.39 (d, $J$ = 5.6 Hz, 6H),1.37 (s, 3H), 1.06 (s, 3H), 0.97 (t, $J$ = 7.4 Hz, 3H). HR-MS: calcd for $C_{23}H_{31}{}^{35}Cl_2NO_3$ ([M+H]$^+$), 440.1759; found, 440.1727. Anal. Calcd for $C_{23}H_{31}Cl_2NO_3$: C, 62.73; H, 7.09; N, 3.18. Found: C, 62.71; H, 7.13; N, 3.16.

#### 5.5.2. (*E*,1*R*,4a*S*,10a*R*)-6,8-Dichloro-1,2,3,4,4a,9,10,10a-octahydro-9-isopropoxyimino-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3e)

Light yellow oil, yield 63%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.11 (br s, 1H), 4.47–4.41 (m, 1H), 4.09 (br s, 1H), 2.99 (dd of ABX system, $J$ = 18.5, 13.0 Hz, 1H), 2.39 (dd of ABX system, $J$ = 18.5, 6.4 Hz, 1H), 2.14 (d, $J$ = 14.9 Hz, 1H), 2.09 (dd of ABX system, $J$ = 13.0, 6.4 Hz, 1H), 1.79–1.69 (m, 4H), 1.62–1.59 (m, 1H), 1.40 (d, $J$ = 6.9 Hz, 6H), 1.37 (s, 3H), 1.35 (d, $J$ = 6.2 Hz, 3H), 1.29 (d, $J$ = 6.2 Hz, 3H), 1.06(s, 3H). HR-MS: calcd for $C_{23}H_{31}{}^{35}Cl_2NO_3$ ([M+H]$^+$), 440.1759; found, 440.1740. Anal. Calcd for

$C_{23}H_{31}Cl_2NO_3$: C, 62.73; H, 7.09; N, 3.18. Found: C, 62.47; H, 7.14; N, 3.02.

#### 5.5.3. (*E*,1*R*,4a*S*,10a*R*)-9-(Isopentyloxy)imino-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3i)

Light yellow oil, yield 24%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.11 (br s, 1H), 4.25 (m, 2H), 4.09 (m, 1H), 3.01 (dd of ABX system, $J$ = 18.5, 13.0 Hz, 1H), 2.40 (dd of ABX system, $J$ = 18.5, 6.4 Hz, 1H), 2.14 (d, $J$ = 12.0 Hz, 1H), 2.09 (dd of ABX system, $J$ = 13.0, 6.4 Hz, 1H), 1.79–1.58 (m, 8H), 1.39 (d, $J$ = 6.0 Hz, 6H), 1.37 (s, 3H), 1.06 (s, 3H), 0.95 (d, $J$ = 6.5 Hz, 3H), 0.94 (d, $J$ = 6.5 Hz, 3H).

Anal. Calcd for $C_{25}H_{35}Cl_2NO_3$: C, 64.10; H, 7.53; N, 2.99. Found: C, 63.95; H, 7.61; N, 2.85.

#### 5.5.4. (*E*,1*R*,4a*S*,10a*R*)-9-(Cyclopropylmethoxy)imino-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethyl phenanthrene-1-carboxylic acid (3j)

Colorless oil, yield 43%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.12 (br s, 1H), 4.09–3.97 (m, 3H), 3.04 (dd of ABX system, $J$ = 18.5, 13.0 Hz, 1H), 2.45 (dd of ABX system, $J$ = 18.5, 6.4 Hz, 1H), 2.14 (d, $J$ = 13.4 Hz, 1H), 2.10 (dd of ABX system, $J$ = 13.0, 6.4 Hz, 1H), 1.79–1.72 (m, 4H), 1.62 (m, 1H), 1.40–1.38 (m, 9H), 1.25 (m, 1H), 1.07 (s, 3H), 0.58–0.54 (m, 2H), 0.39–0.32 (m, 1H), 0.31–0.27 (m, 1H).

Anal. Calcd for $C_{24}H_{31}Cl_2NO_3{\cdot}1/4H_2O$: C, 63.09; H, 6.95; N, 3.07. Found: C, 62.92; H, 6.88; N, 3.09.

#### 5.5.5. (*E*,1*R*,4a*S*,10a*R*)-9-(Cyclohexylmethoxy)imino-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3k)

Light yellow oil, yield 50%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.12 (br s, 1H), 4.05 (m, 2H), 3.95 (dd of ABX system, $J$ = 10.6, 7.1 Hz, 1H), 3.03 (dd of ABX system, $J$ = 18.5, 13.0 Hz, 1H), 2.40 (dd of ABX system, $J$ = 18.5, 6.5 Hz, 1H), 2.14 (d, $J$ = 12.2 Hz, 1H), 2.09 (dd of ABX system, $J$ = 13.0, 6.5 Hz, 1H), 1.83–1.55 (m, 10H), 1.40 (d, $J$ = 6.5 Hz, 6H), 1.37 (s, 3H), 1.27–1.17 (m, 4H), 1.06 (s, 3H), 0.98 (m, 2H).

Anal. Calcd for $C_{27}H_{37}Cl_2NO_3{\cdot}1/4H_2O$: C, 64.99; H, 7.57; N, 2.81. Found: C, 65.06; H, 7.45; N, 2.79.

#### 5.5.6. (*E*,1*R*,4a*S*,10a*R*)-9-(Heptyloxy)imino-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3l)

Light yellow oil, yield 42%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.11 (br s, 1H), 4.25–4.07 (m, 3H), 3.02 (dd of ABX system, $J$ = 18.5, 13.0 Hz, 1H), 2.41 (dd of ABX system, $J$ = 18.5, 6.4 Hz, 1H), 2.14 (d, $J$ = 12.1 Hz, 1H), 2.08 (dd of ABX system, $J$ = 13.0, 6.4 Hz, 1H), 1.79–1.62 (m, 6H), 1.60 (m, 1H), 1.40–1.33 (m, 17H), 1.06 (s, 3H), 0.88 (t, $J$ = 6.7 Hz, 3H). HR-MS: calcd for $C_{27}H_{39}{}^{35}Cl_2NO_3$ ([M+H]$^+$), 496.2385; found, 496.2377.

Anal. Calcd for $C_{27}H_{39}Cl_2NO_3$: C, 65.31; H, 7.92; N, 2.82. Found: C, 65.75; H, 7.85; N, 2.85.

### 5.6. Preparation of compounds 3c and 3h (Method D)

A mixture of the methyl ester **5c**/**5h** (0.048 mmol), KOH (54 mg, 0.96 mmol) and 18-crown ether-6 (63 mg, 0.21 mmol) in MeOH (1 mL) was stirred at 145 °C for 70 min under microwave irradiation, then cooled, and evaporated in vacuo. The residue was diluted with water (10 mL), acidified with 2 N HCl, and extracted with AcOEt. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and evaporated in vacuo. The residue was purified by flash chromatography using *n*-hexane/ethyl acetate as the eluent to afford **3c** and **3h**.

#### 5.6.1. (*E*,1*R*,4a*S*,10a*R*)-6,8-Dichloro-9-ethoxyimino-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3c)

Yellow oil, yield 57%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.12 (br s, 1H), 4.26 (m, 2H), 4.09 (br s, 1H), 3.00 (dd of ABX system, $J$ = 18.5, 13.1 Hz, 1H), 2.42 (dd of ABX system, $J$ = 18.5, 6.4 Hz, 1H), 2.16–2.07 (m, 2H), 1.79–1.57 (m, 5H), 1.41 (d, $J$ = 6.0 Hz, 6H), 1.37 (s, 3H), 1.35 (t, $J$ = 7.2 Hz, 3H), 1.06 (s, 3H). HR-MS: calcd for $C_{22}H_{29}{}^{35}Cl_2NO_3$ ([M+H]$^+$), 426.1602; found, 426.1602.

Anal. Calcd for $C_{22}H_{29}Cl_2NO_3$: C, 61.97; H, 6.86; N, 3.29. Found: C, 62.28; H, 6.85; N, 2.90.

#### 5.6.2. (*E*,1*R*,4a*S*,10a*R*)-9-((3-Methylbut-2-enyloxy)imino)-6,8-dichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3h)

Yellow oil, yield 57%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.11 (br s, 1H), 5.52 (m, 1H), 4.77–4.67 (m, 2H), 4.08 (br s, 1H), 2.99 (dd of ABX system, $J$ = 18.6, 13.0 Hz, 1H), 2.43 (dd of ABX system, $J$ = 18.5, 6.4 Hz, 1H), 2.16–2.05 (m, 2H), 1.78 (s, 3H), 1.73 (s, 3H), 1.71 (m, 4H), 1.59 (m, 1H), 1.41 (d, $J$ = 6.8 Hz, 6H), 1.36 (s, 3H), 1.07 (s, 3H). Anal. Calcd for $C_{25}H_{33}Cl_2NO_3$: C, 64.37; H, 7.13; N, 3.00. Found: C, 64.47; H, 7.23; N, 2.91.

#### 5.6.3. 13-Isopropyl-12,14-dichloro-7-oxopodocarpe-8,11,13-triene-15-carboxylic acid (1m)

To a solution of $CrO_3$ (30 mg, 0.298 mmol) in $Ac_2O$ (9 mL) and AcOH (2 mL) was added dropwise a suspension of **1b** (100 mg, 0.271 mmol) in AcOH (4 mL) at 0 °C over 10 min. The reaction mixture was stirred at 50 °C for 9 h, then cooled, and poured into ice-water (20 mL), and the whole was extracted with $CHCl_3$ 3 times. The combined organic layer was washed with water, saturated aqueous $NaHCO_3$, and brine, and dried over $Na_2SO_4$. The crude mixture was purified by flash chromatography (*n*-hexane/AcOEt = 4:1) to afford **1m** (38 mg, yield 36%) as a colorless oil. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.22 (br s, 1H), 3.91 (br s, 1H), 2.74–2.64 (m, 2H), 2.6–2.53 (m, 1H), 2.19 (d, $J$ = 12.2 Hz, 1H), 1.82–1.75 (m, 5H), 1.38 (d, $J$ = 7.2 Hz, 6H), 1.33 (s, 3H), 1.15 (s, 3H). HR-MS: calcd for $C_{20}H_{24}{}^{35}Cl_2O_3$ ([M+Na]$^+$), 405.1001; found, 405.1012.

Anal. Calcd for $C_{20}H_{24}Cl_2O_3{\cdot}1/4H_2O$: C, 61.94; H, 6.37. Found: C, 61.74; H, 6.25.

### 5.7. DHAA series of compounds

#### 5.7.1. Dehydroabietic acid methyl ester (1e)

A mixture of dehydroabietic acid **1a** (15 g, 0.050 mol) and concentrated $H_2SO_4$ (24 mL) in MeOH (300 mL) was stirred at 85 °C for 48 h, then cooled, and evaporated in vacuo. The residue was diluted with water (300 mL) and extracted with AcOEt 3 times. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and evaporated in vacuo. The residue was purified by flash chromatography (*n*-hexane/AcOEt = 10:1) to afford **1e** (14.3 g, yield 91%) as a light yellow solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.17 (d, $J$ = 8.1 Hz, 1H), 7.00 (d, $J$ = 8.1 Hz, 1H), 6.89 (s, 1H), 3.67 (s, 3H), 2.89 (m, 2H), 2.83 (m, 1H), 2.30 (d, $J$ = 12.1 Hz, 1H), 2.25 (dd of ABX system, $J$ = 12.4, 2.1 Hz, 1H), 1.89–1.61 (m, 5H), 1.50 (m, 1H), 1.40 (m, 1H), 1.28 (s, 3H), 1.23 (d, $J$ = 6.9 Hz, 6H), 1.22 (s, 3H).

#### 5.7.2. 13-Isopropyl-7-oxopodocarpe-8,11,13-triene-15-carboxylic acid methyl ester (1f, same procedure as for synthesis of 1d)

Light yellow oil, yield 48%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.86 (d, $J$ = 2.1 Hz, 1H), 7.41 (dd, $J$ = 8.2, 2.1 Hz, 1H), 7.29 (d, $J$ = 8.2 Hz, 1H), 3.65(s, 3H), 2.92 (m, 1H), 2.72 (dd, $J$ = 7.3, 3.8 Hz, 2H), 2.38–2.32 (m, 2H), 1.82–1.77 (m, 3H), 1.73–1.64 (m, 2H), 1.34 (s, 3H), 1.26–1.24 (m, 9H).

#### 5.7.3. 13-Isopropyl-7-hydroxyiminepodocarpe-8,11,13-triene-15-carboxylic acid methyl ester (5n, same procedure as for synthesis of 5a)

Colorless solid, yield 79%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.69 (s, 1H, 7.21 m, 2H), 3.66 (s, 3H), 2.91(m, 1H), 2.68–2.65 (m, 2H), 2.36–2.28 (m, 2H), 1.77–1.61 (m, 5H), 1.38 (s, 3H), 1.25 (d, $J$ = 6.9 Hz, 6H), 1.12 (s, 3H).

### 5.8. Synthesis of compounds 5o–s

Starting from compound **5n**, Method **B** was employed to obtain compounds **5o–s**.

#### 5.8.1. (*E*,1*R*,4a*S*,10a*R*)-Methyl 1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-9-methoxyimino-1,4a-dimethylphenanthrene-1-carboxylate (5o)

Colorless oil, yield 91%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.76 (s, 1H), 7.19 (d, $J$ = 1.2 Hz, 2H), 4.00 (s, 3H), 3.64 (s, 3H), 2.91 (m, 1H), 2.56 (m, 2H), 2.32–2.26 (m, 2H), 1.76–1.60 (m, 5H), 1.36 (s, 3H), 1.26 (d, $J$ = 6.9 Hz, 3H), 1.25 (d, $J$ = 6.9 Hz, 3H), 1.10 (s, 3H).

#### 5.8.2. (*E*,1*R*,4a*S*,10a*R*)-Methyl 9-(allyloxy)imino-1,2,3,4,4a, 9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5p)

Light yellow oil, yield 92%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.75 (s, 1H), 7.20 (m, 2H), 6.13–6.04 (m, 1H), 5.33 (dd, $J$ = 17.2, 1.6 Hz, 1H), 5.23 (dd, $J$ = 10.4, 1.6 Hz, 1H), 4.72 (d, $J$ = 5.6 Hz, 2H), 3.64 (s, 3H), 2.92 (m, 1H), 2.63 (m,2H), 2.34–2.27 (m, 2H), 1.76–1.60 (m, 5H), 1.37 (s, 3H), 1.25 (d, $J$ = 7.0 Hz, 6H), 1.11 (s, 3H).

#### 5.8.3. (*E*,1*R*,4a*S*,10a*R*)-Methyl 9-((prop-2-ynyloxy)imino)-1,2,3, 4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5q)

Light yellow oil, yield 70%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.77 (s, 1H), 7.20 (m, 2H), 4.80 (d, $J$ = 2.4 Hz, 2H), 3.65 (s, 3H), 2.91 (m, 1H), 2.63–2.59 (m, 2H), 2.49 (t, $J$ = 2.4 Hz, 1H), 2.33–2.26 (m, 2H), 1.76–1.59 (m, 5H), 1.36 (s, 3H), 1.25 (d, $J$ = 6.9 Hz, 3H), 1.24 (d, $J$ = 6.9 Hz, 3H), 1.11 (s, 3H).

#### 5.8.4. (*E*,1*R*,4a*S*,10a*R*)-Methyl 9-(benzyloxy)imino-1,2,3,4,4a, 9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5r)

Light yellow oil, yield 77%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.79 (s, 1H), 7.40 (m, 5H), 7.22 (m, 2H), 5.28 (s, 2H), 3.64 (s, 3H), 2.92 (m, 1H), 2.65 (m, 2H), 2.36–2.29 (m, 2H), 1.76–1.62 (m, 5H), 1.37 (s, 3H), 1.27 (d, $J$ = 6.9 Hz, 6H), 1.13 (s, 3H).

#### 5.8.5. (*E*,1*R*,4a*S*,10a*R*)-Methyl 9-((3-phenylpropoxy)imino)-1,2,3, 4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (5s)

Colorless oil, 60% Yield. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.78 (s, 1H), 7.33–7.13 (m, 7H), 4.24 (t, $J$ = 6.5 Hz, 2H), 3.65 (s, 3H), 2.92 (m, 1H), 2.76 (m, 2H), 2.65 (m, 2H), 2.31 (m, 2H), 2.07 (m, 2H),1.77 (m, 5H), 1.39 (s, 3H), 1.27 (d, $J$ = 7.0 Hz, 6H), 1.13 (s, 3H).

#### 5.8.6. (*E*,1*R*,4a*S*,10a*R*)-1,2,3,4,4a,9,10,10a-Octahydro-9-(hydroxyimino)-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3n)

Compound **3n** was obtained from **5n** according to Method C. Colorless solid, yield 79%. Mp 270–271 °C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 12.32 (s, 1H), 11.16 (s, 1H), 7.68 (d, $J$ = 1.6 Hz, 1H), 7.24 (d, $J$ = 8.2 Hz, 1H), 7.20 (dd, $J$ = 8.2, 1.6 Hz, 1H), 2.85 (m, 1H), 2.56 (dd of ABX system, $J$ = 18.6, 4.8 Hz, 1H), 2.41 (dd of ABX system, $J$ = 18.6, 13.6 Hz, 1H), 2.30 (d, $J$ = 13.0 Hz, 1H), 2.07 (dd of ABX system, $J$ = 13.6,4.8 Hz, 1H), 1.68–1.63 (m, 4H), 1.48–1.42 (m, 1H), 1.23 (s, 3H), 1.18 (d, $J$ = 6.9 Hz, 6H), 1.03 (s, 3H). HR-MS: calcd for $C_{20}H_{27}NO_3$ ($[M+Na]^+$), 352.1889; found, 352.1885.

Anal. Calcd for $C_{20}H_{27}NO_3 \cdot 1/4H_2O$: C, 71.93; H, 8.30; N, 4.19. Found: C, 72.08; H, 8.31; N, 4.09.

### 5.9. Synthesis of compounds 3o–s (Method A)

#### 5.9.1. (*E*,1*R*,4a*S*,10a*R*)-1,2,3,4,4a,9,10,10a-Octahydro-7-isopropyl-9-methoxyimino-1,4a-dimethylphenanthrene-1-carboxylic acid (3o)

Colorless solid, yield 93%. Mp 108–110 °C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.75 (s, 1H), 7.19 (br s, 2H), 4.02 (s, 3H), 2.90 (m, 1H), 2.65 (m, 2H), 2.26 (m, 2H), 1.76 (m, 4H), 1.64 (m, 1H),1.36 (s, 3H), 1.25 (d, $J$ = 6.9 Hz, 3H), 1.24 (d, $J$ = 6.9 Hz, 3H), 1.10 (s, 3H).

Anal. Calcd for $C_{21}H_{29}NO_3$: C, 73.44; H, 8.51; N, 4.08. Found: C, 73.04; H, 8.55; N, 3.99.

#### 5.9.2. (*E*,1*R*,4a*S*,10a*R*)-9-(Allyloxy)imino-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3p)

Light yellow oil, yield 84%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.73 (s, 1H), 7.18 (m, 2H), 6.14–6.05 (m, 1H), 5.36 (dd, $J$ = 17.3, 1.2 Hz, 1H), 5.23 (dd, $J$ = 10.4, 1.2 Hz, 1H), 4.72 (d, $J$ = 5.6 Hz, 2H), 2.90 (m, 1H), 2.68 (m,2H), 2.31–2.27 (m, 2H), 1.77 (m, 4H), 1.64–1.61 (m, 1H), 1.36 (s, 3H), 1.24 (d, $J$ = 6.9 Hz, 3H), 1.23 (d, $J$ = 6.9 Hz, 3H), 1.11 (s, 3H). HR-MS: calcd for $C_{23}H_{31}NO_3$ ($[M+Na]^+$), 392.2202; found, 392.2155.

Anal. Calcd for $C_{23}H_{31}NO_3$: C, 74.76; H, 8.46; N, 3.79. Found: C, 74.51; H, 8.48; N, 3.69.

#### 5.9.3. (*E*,1*R*,4a*S*,10a*R*)-9-((Prop-2-ynyloxy)imino)-1,2,3,4,4a,9,10, 10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3q)

Red brown oil, yield 57%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.75 (s, 1H), 7.19 (m, 2H), 4.81 (d, $J$ = 2.4 Hz, 2H), 2.90 (m, 1H), 2.69 (m, 2H), 2.50 (t, $J$ = 2.4 Hz, 1H), 2.31–2.26 (m, 2H), 1.77 (br s, 4H), 1.63 (m, 1H), 1.36 (s, 3H), 1.25 (d, $J$ = 6.9 Hz, 3H), 1.24 (d, $J$ = 6.9 Hz, 3H), 1.11 (s, 3H).

Anal. Calcd for $C_{23}H_{29}NO_3 \cdot 1/4H_2O$: C, 74.26; H, 7.99; N, 3.77. Found: C, 74.33; H, 8.01; N, 3.65.

#### 5.9.4. (*E*,1*R*,4a*S*,10a*R*)-9-(Benzyloxy)imino-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3r)

Light yellow oil, yield 91%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.75 (s, 1H), 7.42 (m, 2H), 7.36 (m, 2H), 7.29 (m, 1H), 7.19 (br s, 2H), 5.25 (s, 2H), 2.90 (m, 1H), 2.77 (dd of ABX system, $J$ = 18.8, 5.2 Hz, 1H), 2.66 (dd of ABX system, $J$ = 18.8, 13.2 Hz, 1H), 2.33–2.27 (m, 2H), 1.77 (br s, 4H), 1.62 (m, 1H), 1.36 (s, 3H), 1.25 (d, $J$ = 6.9 Hz, 6H), 1.11 (s, 3H).

Anal. Calcd for $C_{27}H_{33}NO_3$: C, 77.29; H, 7.93; N, 3.34. Found: C, 77.09; H, 7.95; N, 3.32.

#### 5.9.5. (*E*,1*R*,4a*S*,10a*R*)-9-((3-Phenylpropoxy)imino)-1,2,3,4,4a,9, 10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3s)

Colorless oil, 77% Yield. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.78 (s, 1H), 7.31–7.17 (m, 7H), 4.25 (t, $J$ = 6.5 Hz, 2H), 2.93 (m, 1H), 2.75 (m, 3H), 2.64 (dd of ABX system, $J$ = 18.8, 13.2 Hz, 1H), 2.30 (d, $J$ = 5.2 Hz, 2H), 2.08 (m, 2H),1.76 (br s, 4H), 1.64 (m, 1H), 1.38 (s, 3H), 1.28 (d, $J$ = 6.9 Hz, 3H), 1.27 (d, $J$ = 6.9 Hz, 3H), 1.14 (s, 3H). HR-MS: calcd for $C_{29}H_{37}NO_3$ ($[M+H]^+$), 448.2851; found, 448.2832.

Anal. Calcd for $C_{29}H_{37}NO_3$: C, 77.82; H, 8.33; N, 3.13. Found: C, 77.56; H, 8.45; N, 3.12.

#### 5.9.6. 13-Isopropyl-7-oxopodocarpe-8,11,13-triene-15-carboxylic acid (1n, Method C)

Colorless solid, yield 79%. Mp 90–91 °C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.87 (d, $J$ = 2.1 Hz, 1H), 7.40 (dd, $J$ = 8.2, 2.1 Hz, 1H), 7.29 (d, $J$ = 8.2 Hz, 1H), 2.91 (m, 1H), 2.71 (m, 2H), 2.49 (d, $J$ = 15.0 Hz, 1H), 2.36 (d, $J$ = 12.5 Hz, 1H), 1.86–1.77 (m, 4H), 1.64 (m, 1H), 1.35 (s, 3H), 1.26 (s, 3H), 1.24 (d, $J$ = 6.9 Hz, 3H), 1.23 (d, $J$ = 6.9 Hz, 3H). HR-MS: calcd for $C_{20}H_{26}O_3$ ([M+Na]$^+$), 337.1780; found, 337.1781.

Anal. Calcd for $C_{20}H_{26}O_3 \cdot 1/8H_2O$: C, 75.86; H, 8.36. Found: C, 75.71; H, 8.09.

### 5.10. 12-Bromo-DHAA series

#### 5.10.1. (1*R*,4a*S*,10a*R*)-Methyl 6-bromo-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylate (1g)

To a stirred solution of **1e** (13.7 g, 43.8 mmol) in dry $CH_3CN$ (350 mL) was added *N*-bromosuccinimide (NBS, 8.57 g, 48.2 mmol) and Montmorillonite K10 (42.48 g, 0.97 g/mmol) at rt under protection from light. After 24 h, the catalyst was removed by filtration and the solid was washed with AcOEt at least three times. The combined filtrates were washed with saturated aqueous $Na_2SO_3$, brine and dried over $Na_2SO_4$. The crude mixture was purified by flash chromatography (*n*-hexane/AcOEt = 10:1) to afford a mixture of **1g** and **1h** (11.9 g, conversion rate 69%, **1g**/**1h** = 3.1:1) as a yellow solid. Compound **1g**: $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.36 (s, 1H), 6.91 (s, 1H), 3.66 (s, 3H), 3.29–3.22 (m, 1H), 2.85–2.81 (m, 2H), 2.24 (d, $J$ = 12.3 Hz, 1H), 2.18 (dd of ABX system, $J$ = 12.5, 2.1 Hz, 1H), 1.86–1.65 (m, 5H), 1.56–1.34 (m, 2H), 1.27 (s, 3H), 1.21 (d, $J$ = 7.1 Hz, 3H), 1.20 (s, 3H), 1.20 (d, $J$ = 7.1 Hz, 3H).

#### 5.10.2. (1*R*,4a*S*,10a*R*)-Methyl 6-bromo-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethyl-9-oxophenanthrene-1-carboxylate (1i, same procedure as 1d)

Colorless oil, yield 83%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.87 (s, 1H), 7.51 (s, 1H), 3.62 (s, 3H), 3.32–3.22 (m, 1H), 2.68–2.65 (m, 2H), 2.36–2.31 (m, 2H), 1.78–1.67 (m, 4H), 1.64–1.58 (m, 1H), 1.30 (s, 3H), 1.24 (s, 3H), 1.21 (d, $J$ = 7.0 Hz, 3H), 1.20 (d, $J$ = 7.0 Hz, 3H).

#### 5.10.3. (*E*,1*R*,4a*S*,10a*R*)-Methyl 6-bromo-1,2,3,4,4a,9,10,10a-octahydro-9-(hydroxyimino)-7-isopropyl-1,4a-dimethyl phenanthrene-1-carboxylate (5t, same procedure as 5a)

Light yellow solid, yield 97%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.75 (s, 1H), 7.52 (s, 1H), 3.65 (s, 3H), 3.30 (m, 1H), 2.64–2.62 (m, 2H), 2.29 (dd of ABX system, $J$ = 10.4, 8.1 Hz, 1H), 2.24 (d, $J$ = 12.4 Hz, 1H), 1.77–1.62 (m, 5H), 1.36 (s, 3H), 1.25 (d, $J$ = 6.8 Hz, 3H), 1.23 (d, $J$ = 6.8 Hz, 3H), 1.12 (s,3H).

#### 5.10.4. (*E*,1*R*,4a*S*,10a*R*)-6-Bromo-1,2,3,4,4a,9,10,10a-octahydro-9-(hydroxyimino)-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3t, Method C)

Colorless solid, yield 52%. Mp 268–271 °C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.56 (s, 1H), 7.42 (s, 1H), 3.24 (m, 1H), 2.84 (dd of ABX system, $J$ = 19.2, 5.0 Hz, 1H), 2.69 (dd of ABX system, $J$ = 19.2, 13.4 Hz, 1H), 2.32 (dd of ABX system, $J$ = 13.4, 5.0 Hz, 1H), 2.24 (d, $J$ = 12.7 Hz,1H), 1.78 (m, 4H), 1.63–1.57 (m, 1H), 1.39 (s, 3H), 1.13 (d, $J$ = 7.2 Hz, 6H), 1.12 (s,3H).

HR-MS: calcd for $C_{20}H_{26}{}^{79}BrNO_3$ ([M+Na]$^+$), 408.1174; found, 408.1165.

### 5.11. Synthesis of compounds 5u–v (Method B)

#### 5.11.1. (*E*,1*R*,4a*S*,10a*R*)-Methyl 6-bromo-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-9-methoxyimino-1,4a-dimethyl phenanthrene-1-carboxylate (5u)

Colorless oil, yield 73%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.80 (s, 1H), 7.40 (s, 1H), 3.99 (s, 3H), 3.62 (s, 3H), 3.29 (m, 1H), 2.54 (m, 2H), 2.27–2.20 (m, 2H), 1.78–1.69 (m, 4H), 1.62 (m, 1H), 1.34 (s, 3H), 1.27 (d, $J$ = 6.8 Hz, 3H), 1.24 (d, $J$ = 6.8 Hz, 3H), 1.09 (s, 3H).

#### 5.11.2. (*E*,1*R*,4a*S*,10a*R*)-Methyl 9-(allyloxy)imino-6-bromo-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethyl phenanthrene-1-carboxylate (5v)

Light yellow oil, yield 70%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.80 (s, 1H), 7.40 (s, 1H), 6.12–6.02 (m, 1H), 5.33 (m, 1H), 5.23 (m, 1H), 4.71 (dt, $J$ = 5.8, 1.3 Hz, 2H), 3.64 (s, 3H), 3.29 (m, 1H), 2.58 (d, $J$ = 9.4 Hz, 2H), 2.29–2.21 (m, 2H), 1.75–1.69 (m, 4H), 1.65–1.58 (m, 1H), 1.35 (s, 3H), 1.26 (d, $J$ = 6.9 Hz, 3H), 1.23 (d, $J$ = 6.9 Hz, 3H), 1.10 (s, 3H).

### 5.12. Synthesis of compounds 3u–v (Method A)

#### 5.12.1. (*E*,1*R*,4a*S*,10a*R*)-6-Bromo-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-9-methoxyimino-1,4a-dimethylphenanthrene-1-carboxylic acid (3u)

Colorless solid, yield 90%. Mp 128–131.5 °C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.80 (s, 1H), 7.39 (s, 1H), 4.01 (s, 3H), 3.29 (m, 1H), 2.69–2.54 (m, 2H), 2.24 (m, 2H), 1.76 (m, 4H), 1.61 (m, 1H), 1.34 (s, 3H), 1.27 (d, $J$ = 6.9 Hz, 3H), 1.24 (d, $J$ = 6.9 Hz, 3H), 1.10 (s, 3H). HR-MS: calcd for $C_{21}H_{28}{}^{79}BrNO_3$ ([M+Na]$^+$), 444.1151; found, 444.1152.

Anal. Calcd for $C_{21}H_{28}BrNO_3 \cdot 1/4H_2O$: C, 59.09; H, 6.73; N, 3.28. Found: C, 58.91; H, 6.60; N, 3.16.

#### 5.12.2. (*E*,1*R*,4a*S*,10a*R*)-9-(Allyloxy)imino-6-bromo-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3v)

Light yellow oil, yield 72%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.79 (s, 1H), 7.39 (s, 1H), 6.13–6.03 (m, 1H), 5.33 (m, 1H), 5.23 (m, 1H), 4.72 (dt, $J$ = 5.8, 1.3 Hz, 2H), 3.29 (m, 1H), 2.74–2.56 (m, 2H), 2.27–2.21 (m, 2H), 1.76 (m, 4H), 1.61(m, 1H), 1.34 (s, 3H), 1.26 (d, $J$ = 6.8 Hz, 3H), 1.23 (d, $J$ = 6.8 Hz, 3H), 1.10 (s, 3H).

Anal. Calcd for $C_{23}H_{30}BrNO_3$: C, 61.61; H, 6.74; N, 3.12. Found: C, 61.39; H, 6.71; N, 2.75.

#### 5.12.3. (1*R*,4a*S*,10a*R*)-6-Bromo-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethyl-9-oxophenanthrene-1-carboxylic acid (1p)

Compound **1i** (84 mg, 0.206 mmol) was treated with KOBu$^t$ (3.1 mmol) in DMSO (3.1 mL) at rt for about 40 min. The reaction mixture was poured into ice-water, acidified with 2 N HCl and extracted with AcOEt. The combined organic layer was washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and evaporated in vacuo. The crude mixture was purified by flash chromatography (*n*-hexane/AcOEt = 2:1) to afford **1p** (12 mg, 15% yield) as a yellow oil. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.90 (s, 1H), 7.53 (s, 1H), 3.31 (m, 1H), 2.69 (m, 2H), 2.48 (d, $J$ = 15.2 Hz, 1H), 2.31 (d, $J$ = 12.6 Hz, 1H), 1.81 (m, 4H), 1.64 (m, 1H), 1.34 (s, 3H), 1.27 (s, 3H), 1.25 (d, $J$ = 6.9 Hz, 3H), 1.22 (d, $J$ = 6.9 Hz, 3H). HR-MS: calcd for $C_{20}H_{25}{}^{79}BrO_3$ ([M+H]$^+$), 393.1065; found, 393.1034. Anal. Calcd for $C_{20}H_{25}BrO_3$: C, 61.07; H, 6.41. Found: C, 61.30; H, 6.49.

### 5.13. 11,12,14-Trichloro-DHAA series

#### 5.13.1. 11,12,14-Trichlorodehydroabietic acid (1j)

To a solution of **1a** (2.008 g, 6.689 mmol) in $CCl_4$ (7 mL) was added $FeCl_3$ (503 mg, 3.10 mmol) and 1% DDQ on $SiO_2$ (119.1 mg). The reaction mixture was stirred at rt, and a solution of $Cl_2$ in $CCl_4$ (2.4 M, 40 mL) was added in one portion at 0 °C in the dark. Stirring was continued at rt for 17 h, then the solution was poured into a saturated aqueous solution of $Na_2SO_3$ (100 mL), and extracted with $CHCl_3$ (70 × 3 mL). The organic layer was washed with water (20 mL), dried over $Na_2SO_4$ and evaporated in vacuo to give a residue, which was purified by flash chromatography (*n*-hexane/AcOEt = 7:1) to afford **1j** (0.973 g, 2.34 mmol, yield 35%) as a colorless powder. Mp: 252.8–253.0 °C (recrystallized from AcOEt/*n*-hexane). Colorless needles.

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 4.01 (m, 1H), 3.45 (d, $J$ = 1.24 Hz, 1H), 2.90–2.81 (m, 2H), 2.06 (d, $J$ = 11.2 Hz, 1H), 1.90–1.60 (m, 5H), 1.59–1.51 (m, 1H), 1,48 (s, 3H), 1.38 (d, $J$ = 7.20 Hz, 6H), 1.29 (s, 3H), 1.25–1.10 (m, 1H). $^{13}$C NMR ($CDCl_3$, 100 MHz): 184.9, 146.1, 141.3, 134.6, 48.2, 46.7, 40.9, 36.1, 34.9, 32.3, 21.5, 19.2, 19.0, 18.6, 16.9. HR-MS: calcd for $C_{20}H_{24}{}^{35}Cl_3O_2$ $[M\text{-}H]^-$ 401.0842; found, 401.0844. Anal. Calcd for $C_{20}H_{25}Cl_3O_2$: C; 59.49, H; 6.24. Found: C; 59.24, H; 6.24.

#### 5.13.2. 11,12,14-Trichlorodehydroabietic acid methyl ester (1k)

To a solution of **1j** (300 mg, 0.74 mmol) in MeOH (1 mL) and PhMe (2 mL) was added dropwise 2.0 M $TMSCHN_2$ in $Et_2O$ (0.5 mL, 1 mmol) at rt over 5 min, and the whole was stirred at rt for 30 min. Excess $TMSCHN_2$ was quenched with AcOH, then the reaction mixture was evaporated in vacuo, and the residue was purified by flash chromatography (*n*-hexane only to *n*-hexane/AcOEt = 10:1) to afford **1k** (292 mg, yield 94%) as a colorless solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 4.02 (m, 1H), 3.69 (s, 3H), 3.47 (m, 1H), 2.89–2.74 (m, 2H), 2.07 (d, $J$ = 11.6 Hz, 1H), 1.76–1.58 (m, 6H), 1.48 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.29 (s, 3H), 1.15 (m, 1H).

#### 5.13.3. (1*R*,4a*S*,10a*R*)-Methyl 5,6,8-trichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethyl-9-oxophenanthrene-1-carboxylate (1l)

To a solution of $CrO_3$ (80 mg, 0.8 mmol) in $Ac_2O$ (2 mL) and AcOH (1 mL) was added dropwise a suspension of the methyl ester **1k** (292 mg, 0.7 mmol) in AcOH (2 mL) at 0 °C over 10 min. The reaction mixture was stirred at 50 °C for 9 h, then cooled, poured into ice-water (40 mL) and extracted with $CHCl_3$ 3 times. The combined organic layer was washed with water, saturated $NaHCO_3$, and brine, and dried over $Na_2SO_4$. The crude mixture was purified by flash chromatography (*n*-hexane/AcOEt = 12:1) to afford **1l** (247 mg, yield 82%) as a yellow solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 4.03 (br s, 1H), 3.67 (s, 3H), 3.47 (m, 1H), 2.73–2.63 (m, 2H), 1.76–1.65 (m, 5H), 1.42 (s, 3H), 1.40 (s, 6H), 1.32 (s, 3H).

#### 5.13.4. (*E*,1*R*,4a*S*,10a*R*)-Methyl 5,6,8-trichloro-1,2,3,4,4a,9,10,10a-octahydro-9-(hydroxyimino)-7-isopropyl-1,4a-dimethyl-phenanthrene-1-carboxylate (5w)

A mixture of the methyl ester **1l** (179 mg, 0.415 mmol), pyridine (0.05 mL), and $NH_2OH{\cdot}HCl$ (50 mg, 0.72 mmol) in EtOH (1 mL) was stirred at 100 °C for 3 h, then cooled, and evaporated in vacuo. The residue was purified by flash chromatography (*n*-hexane/AcOEt = 5:1) to afford **5w** (156 mg, yield 84%) as a colorless solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 4.09 (br s, 1H), 3.68 (s, 3H), 3.42 (m, 1H), 3.00 (dd of ABX system, $J$ = 18.7, 13.8 Hz, 1H), 2.36 (dd of ABX system, $J$ = 18.7, 5.6 Hz, 1H), 2.23 (dd of ABX system, $J$ = 13.8, 5.6 Hz, 1H), 1.69–1.63 (m, 5H), 1.44 (d, $J$ = 6.5 Hz, 6H),1.36 (s, 3H), 1.25 (s, 3H).

### 5.14. General procedure for preparation of compounds 5x–y

To a solution of compound **5w** (0.1 mmol) in 2 mL DMF was added NaH (6 mg, 0.15 mmol, 60% in mineral oil) at about 0 °C, in a flask fitted with a $CaCl_2$ tube. The mixture was stirred at 0 °C for 30 min, then the corresponding bromide (0.15 mmol) was added. The solution was gradually warmed to rt and stirred overnight. The reaction was quenched with saturated aqueous $NH_4Cl$, and then the whole was extracted with AcOEt. The combined organic layer was washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and evaporated in vacuo. The residue was purified by flash chromatography using *n*-hexane/ethyl acetate as the eluent to afford **5x**–**y**.

#### 5.14.1. (*E*,1*R*,4a*S*,10a*R*)-Methyl 5,6,8-trichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-9-methoxyimino-1,4a-dimethyl-phenanthrene-1-carboxylate (5x)

Yellow oil, yield 99%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 4.07 (br s, 1H), 3.97 (s, 3H), 3.67 (s, 3H), 3.40 (m, 1H), 2.92 (dd of ABX system, $J$ = 18.5, 13.7 Hz, 1H), 2.28 (dd of ABX system, $J$ = 18.5, 5.6 Hz, 1H), 2.18 (dd of ABX system, $J$ = 13.7, 5.6 Hz, 1H), 1.69–1.39 (m, 5H), 1.42 (m, 6H), 1.35 (s, 3H), 1.26 (s, 3H).

#### 5.14.2.(*E*,1*R*,4a*S*,10a*R*)-Methyl9-(allyloxy)imino-5,6,8-trichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethyl phenanthrene-1-carboxylate(5y)

Colorless prisms, yield 100%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 6.09–6.00 (m, 1H), 5.26 (m, 2H), 4.67 (m, 2H), 4.09 (br s, 1H), 3.67 (s, 3H), 3.41 (d, $J$ = 12.4 Hz, 1H), 2.96 (dd of ABX system, $J$ = 18.5, 13.7 Hz, 1H), 2.31 (dd of ABX system, $J$ = 18.5, 5.7 Hz, 1H), 2.20 (dd of ABX system, $J$ = 13.7, 5.7 Hz, 1H), 1.69–1.62 (m, 5H), 1.42 (d, $J$ = 6.5 Hz, 6H), 1.36 (s, 3H), 1.27 (s, 3H).

### 5.15. General procedure for preparation of compounds 3w–y

A mixture of the methyl ester **5w**–**y** (0.048 mmol), KOH (54 mg, 0.96 mmol) and 18-crown ether-6 (63 mg, 0.21 mmol) in MeOH (1 mL) was stirred at 145 °C for 70 min under microwave irradiation, then cooled, and evaporated in vacuo. The residue was diluted with water (10 mL), and the mixture was acidified with 2 N HCl, then extracted with AcOEt. The combined organic layer was washed with brine, dried over $Na_2SO_4$, filtered, and evaporated in vacuo. The residue was purified by flash chromatography using *n*-hexane/ethyl acetate (2/1) as the eluent to afford **3w**–**y**.

#### 5.15.1. (*E*,1*R*,4a*S*,10a*R*)-5,6,8-Trichloro-1,2,3,4,4a,9,10,10a-octahydro-9-(hydroxyimino)-7-isopropyl-1,4a-dimethylphenanthrene-1-carboxylic acid (3w)

light yellow solid, yield 86%. $^1$H NMR (DMSO-$d_6$, 400 MHz): $\delta$ 4.05 (br s, 1H), 3.40 (m, 1H), 2.85 (dd of ABX system, $J$ = 18.6, 14.0 Hz, 1H), 2.23 (dd of ABX system, $J$ = 18.6, 5.3 Hz, 1H), 2.07 (dd of ABX system, $J$ = 14.0, 5.3 Hz, 1H), 1.62–1.57 (m, 5H), 1.37 (d, $J$ = 6.9 Hz, 6H), 1.23 (s, 3H), 1.19 (s, 3H).

HR-MS: calcd for $C_{20}H_{24}{}^{35}Cl_3NO_3$ ($[M+H]^+$), 432.0900; found, 432.0886.

Anal. Calcd for $C_{20}H_{24}Cl_3NO_3$: C, 55.51; H, 5.59; N, 3.24. Found: C, 55.41; H, 5.66; N, 3.11.

#### 5.15.2. (*E*,1*R*,4a*S*,10a*R*)-5,6,8-Trichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-9-methoxyimino-1,4a-dimethylphenanthrene-1-carboxylic acid (3x)

Yellow oil, yield 56%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 4.06 (br s, 1H), 3.99 (s, 3H), 3.42 (d, $J$ = 13.2 Hz, 1H), 2.95 (dd of ABX system, $J$ = 18.6, 13.8 Hz, 1H), 2.43 (dd of ABX system, $J$ = 18.6, 5.6 Hz, 1H), 2.18 (dd of ABX system, $J$ = 13.8, 5.6 Hz, 1H), 1.70 (m, 5H), 1.42 (br s, 6H), 1.36 (s, 3H), 1.27 (s, 3H).

HR-MS: calcd for $C_{21}H_{26}{}^{35}Cl_3NO_3$ ([M+Na]$^+$), 468.0876; found, 468.0874. Anal. Calcd for $C_{21}H_{26}Cl_3NO_3 \cdot 1/4H_2O$: C, 55.89; H, 5.92; N, 3.10. Found: C, 55.90; H, 6.02; N, 2.92.

#### 5.15.3. (*E*,1*R*,4a*S*,10a*R*)-9-(Allyloxy)imino-5,6,8-trichloro-1,2,3,4,4a,9,10,10a-octahydro-7-isopropyl-1,4a-dimethyl phenanthrene-1-carboxylic acid (3y)

Light yellow oil, yield 56%. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 6.10–6.01 (m, 1H), 5.34–5.21 (m, 2H), 4.68 (m, 2H), 4.06 (br s, 1H), 3.42 (d, $J$ = 13.2 Hz, 1H), 2.98 (dd of ABX system, $J$ = 18.6, 13.8 Hz, 1H), 2.46 (dd of ABX system, $J$ = 18.6, 5.6 Hz, 1H), 2.19 (dd of ABX system, $J$ = 13.8, 5.6 Hz, 1H), 1.70 (m, 5H), 1.42 (d, $J$ = 6.4 Hz, 6H), 1.36 (s, 3H), 1.28 (s, 3H). Anal. Calcd for $C_{23}H_{28}Cl_3NO_3$: C, 58.42; H, 5.97; N, 2.96. Found: C, 58.71; H, 6.08; N, 2.70.

### 5.16. Podocarpate series

#### 5.16.1. Podocarpic acid methyl ester (6a)

To a solution of podocarpic acid **2** (500 mg, 1.82 mmol) in MeOH (3 mL) and PhMe (6 mL) was added dropwise 2.0 M $TMSCHN_2$ (2.4 mmol) in $Et_2O$ (1.2 mL) at rt over 5 min, and the whole was stirred at rt for 1 h. Excess $TMSCHN_2$ was quenched with AcOH, then the reaction mixture was evaporated in vacuo, and the residue (**6a**) was used for the following procedures without further purification. Mp 213.3–214.5 °C. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.94 (s, 1H), 6.78 (d, $J$ = 8.2 Hz, 1H), 6.63 (d, $J$ = 2.2 Hz, 1H), 6.48 (dd, $J$ = 8.2, 2.2 Hz, 1H), 3.58 (s, 3H), 2.72 (dd of ABX system, $J$ = 15.9, 4.3 Hz, 1H), 2.61 (dt, $J$ = 12.5, 5.7 Hz, 1H), 2.14–2.04 (m, 3H), 1.92–1.75 (m, 2H), 1.54 (m, 1H), 1.49 (d, $J$ = 11.8 Hz, 1H), 1.26 (dt, $J$ = 13.2, 3.8 Hz, 1H), 1.21 (s, 3H), 1.08 (dt, $J$ = 13.2, 4.0 Hz, 1H), 0.91 (s, 3H). HR-MS: calcd for $C_{18}H_{24}O_3$ ([M+Na]$^+$), 311.1623; found, 311.1615.

#### 5.16.2. 12-Acetoxypodocarpic acid methyl ester (6b)

A solution of **6a** (4.03 g, 0.014 mol), $CH_3COONa$ (0.976 g, 11.9 mmol) in 80 mL $Ac_2O$ was refluxed for 3 h. After removal of the excess $Ac_2O$ under reduced pressure, the residue was dissolved in ether. The organic layer was washed with 5% $NaHCO_3$, dried over $Na_2SO_4$ and evaporated to dryness. Recrystallization from MeOH-$H_2O$ afforded **6b** (4.16 g, 90% yield) as a colorless solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.03 (d, $J$ = 8.3 Hz, 1H), 6.95 (d, $J$ = 2.4 Hz, 1H), 6.81 (dd, $J$ = 8.3, 2.4 Hz, 1H), 3.66 (s, 3H), 2.92–2.87 (m, 1H), 2.81–2.72 (m, 1H), 2.29 (m, 1H), 2.26 (s,3H), 2.20–2.16 (m, 2H), 2.04–1.91 (m, 2H), 1.62 (m, 1H), 1.53 (dd of ABX system, $J$ = 12.3, 1.6 Hz, 1H), 1.40 (td, $J$ = 13.3, 4.2 Hz, 1H), 1.27 (s, 3H), 1.09 (td, $J$ = 13.5, 4.2 Hz, 1H), 1.03 (s, 3H).

#### 5.16.3. 12-Acetoxy-7-oxo-podocarpic acid methyl ester (6c)

To a solution of $CrO_3$ (1.468 g, 14.7 mmol) in $Ac_2O$ (40 mL) and AcOH (30 mL) was added dropwise a suspension of the methyl ester **6b** (4.043 g, 12.2 mmol) in AcOH (15 mL) at 0 °C over 10 min. The reaction mixture was stirred at rt overnight, and poured into ice-water. The whole was extracted with AcOEt 3 times. The combined organic layer was washed with water, saturated $NaHCO_3$, and brine, dried over $Na_2SO_4$. The crude mixture was purified by flash chromatography (*n*-hexane/AcOEt = 4:1) to afford **6c** (3.597 g, yield 85%) as a colorless solid. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 8.06 (d, $J$ = 8.6 Hz, 1H), 7.12 (d, $J$ = 2.2 Hz, 1H), 7.03 (dd, $J$ = 8.6, 2.2 Hz, 1H), 3.69 (s, 3H), 3.21 (dd of ABX system, $J$ = 18.0, 14.5 Hz, 1H), 2.98 (dd of ABX system, $J$ = 18.0, 3.2 Hz, 1H), 2.32–2.26 (m, 2H), 2.31 (s,3H), 2.04 (m, 2H), 1.70 (m, 1H), 1.53 (td, $J$ = 13.4, 4.2 Hz, 1H), 1.25 (s, 3H), 1.13 (td, $J$ = 13.6, 4.0 Hz, 1H), 1.11 (s, 3H).

### 5.17. Synthesis of compounds 6d and 6e

A mixture of the methyl ester **6c** (39 mg, 0.113 mmol), pyridine (25 μL), and $NH_2OH \cdot HCl$ (13 mg, 0.187 mmol) in EtOH (1 mL) was stirred at 100 °C for 3 h, then cooled, and evaporated in vacuo. The residue was purified by flash chromatography (*n*-hexane/AcOEt = 2:1–1:1) to afford **6d** (7 mg, 17% yield) as a colorless oil and **6e** (30 mg, 83% yield) as a colorless solid.

#### 5.17.1. (*E*,1*S*,4a*S*)-Methyl 6-acetoxy-1,2,3,4,4a,9,10,10a-octahydro-9-(hydroxyimino)-1,4a-dimethylphenanthrene-1-carboxylate (6d)

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.96 (br s, 1H), 7.94 (d, $J$ = 8.6 Hz, 1H), 7.04 (d, $J$ = 2.3 Hz, 1H), 6.93 (dd, $J$ = 8.6, 2.3 Hz, 1H), 3.71 (s, 3H), 3.42 (dd of ABX system, $J$ = 18.8, 4.4 Hz, 1H), 3.07 (dd of ABX system, $J$ = 18.8, 13.9 Hz, 1H), 2.30 (s,3H), 2.25 (m, 2H), 2.00 (m, 1H), 1.75–1.66 (m, 2H), 1.53 (td, $J$ = 13.4, 4.1 Hz, 1H), 1.32 (s, 3H), 1.11 (td, $J$ = 13.6, 3.8 Hz, 1H), 1.01 (s, 3H).

#### 5.17.2. (*E*,1*S*,4a*S*)-Methyl 1,2,3,4,4a,9,10,10a-octahydro-6-hydroxy-9-(hydroxyimino)-1,4a-dimethylphenanthrene-1-carboxylate (6e)

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.80 (d, $J$ = 8.6 Hz, 1H), 6.80 (d, $J$ = 2.5 Hz, 1H), 6.67 (dd, $J$ = 8.6, 2.5 Hz, 1H), 3.71 (s, 3H), 3.42 (dd of ABX system, $J$ = 18.7, 4.4 Hz, 1H), 3.04 (dd of ABX system, $J$ = 18.7, 13.8 Hz, 1H), 2.25 (m, 2H), 2.00 (m, 1H), 1.73–1.64 (m, 2H), 1.49 (td, $J$ = 13.2, 4.0 Hz, 1H), 1.31 (s, 3H), 1.09 (td, $J$ = 13.4, 3.8 Hz, 1H), 0.98 (s, 3H).

### 5.18. Synthesis of compounds 6g and 6h

A solution of **6e** (30 mg, 0.095 mmol) and $Cs_2CO_3$ (62 mg, 0.189 mmol) in 1 mL DMF was stirred at r.t for 30 min, then 1-bromo-3-phenylpropane (25 μL, 0.164 mmol) was added. The mixture was stirred overnight at rt, then poured into ice-water, and extracted with AcOEt 3 times. The combined organic layer was washed with water, and brine, and dried over $Na_2SO_4$. The crude mixture was purified by flash chromatography (*n*-hexane/AcOEt = 4:1) to afford **6g** (24 mg, 46% yield) as a colorless oil and **6h** (30 mg, 46% yield) as a yellow solid.

#### 5.18.1. (*E*,1*S*,4a*S*,10a*R*)-Methyl 9-((3-phenylpropoxy)imino)-6-(3-phenylpropoxy)-1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethylphenanthrene-1-carboxylate (6g)

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.97 (d, $J$ = 8.7 Hz, 1H), 7.35–7.28 (m, 4H), 7.25–7.23 (m, 6H), 6.86 (d, $J$ = 2.4 Hz, 1H), 6.76 (dd, $J$ = 8.7, 2.4 Hz, 1H), 4.25 (t, $J$ = 6.4 Hz, 2H), 4.01 (t, $J$ = 6.2 Hz, 2H), 3.74 (s, 3H), 3.45–3.39 (m, 3H), 3.04 (dd of ABX system, $J$ = 18.6, 13.8 Hz, 1H), 2.87–2.78 (m, 4H), 2.31 (m, 2H), 2.24–1.99 (m, 5H), 1.76–1.70 (m, 2H), 1.54 (m, 1H), 1.34 (s, 3H), 1.14 (m, 1H), 1.04 (s, 3H).

#### 5.18.2. (*E*,1*S*,4a*S*,10a*R*)-Methyl 6-(3-phenylpropoxy)-1,2,3,4,4a,9,10,10a-octahydro-9-(hydroxyimino)-1,4a-dimethylphenanthrene-1-carboxylate (6h)

$^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.85 (d, $J$ = 8.8 Hz, 1H), 7.32–7.28 (m, 2H), 7.23–7.19 (m, 3H), 6.86 (d, $J$ = 2.5 Hz, 1H), 6.75 (dd, $J$ = 8.8, 2.5 Hz, 1H), 3.99 (t, $J$ = 6.3 Hz, 2H), 3.72 (s, 3H), 3.45 (dd of ABX system, $J$ = 18.7, 4.4 Hz, 1H), 3.07 (dd of ABX system, $J$ = 18.7, 13.9 Hz, 1H), 2.82 (t, $J$ = 7.8 Hz, 2H), 2.30 (m, 2H), 2.15–2.08 (m, 2H), 2.00 (m, 1H), 1.76–1.67 (m, 2H), 1.53 (td, $J$ = 13.3, 4.0 Hz, 1H), 1.33 (s, 3H), 1.12 (td, $J$ = 13.5, 3.8 Hz, 1H), 1.01 (s, 3H).

#### 5.18.3. (*E*,1*S*,4a*S*,10a*R*)-6-(3-Phenylpropoxy)-1,2,3,4,4a,9,10,10a-octahydro-9-(hydroxyimino)-1,4a-dimethylphenanthrene-1-carboxylic acid (4a)

Compound **6h** (197 mg, 0.452 mmol) was treated with $KOBu^t$ (6.78 mmol) in DMSO (6 mL) at 60 °C for about 2 h. Then the reaction mixture was poured into ice-water, acidified with 2 N HCl, and extracted with AcOEt. The combined organic layer was washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and evaporated in vacuo. The crude mixture was purified by flash chromatography (*n*-hexane/AcOEt = 2:1) to afford **4a** (170 mg, 89% yield) as a light yellow solid. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.76 (d, $J$ = 8.7 Hz, 1H), 7.31–7.27 (m, 2H), 7.20–7.18 (m, 3H), 6.86 (d, $J$ = 2.5 Hz, 1H), 6.76 (dd, $J$ = 8.7, 2.5 Hz, 1H), 3.98 (t, $J$ = 6.3 Hz, 2H), 3.40 (dd of ABX system, $J$ = 19.1, 4.8 Hz, 1H), 3.27 (dd of ABX system, $J$ = 19.1, 13.5 Hz, 1H), 2.81 (t, $J$ = 7.3 Hz, 2H), 2.30 (m, 2H), 2.14–2.00 (m, 3H), 1.77–1.68 (m, 2H), 1.53 (td, $J$ = 13.3, 4.0 Hz, 1H), 1.38 (s, 3H), 1.12 (td, $J$ = 13.4, 3.4 Hz, 1H), 1.10 (s, 3H). HR-MS: calcd for $C_{26}H_{31}NO_4$ ($[M+H]^+$), 422.2331; found, 422.2351.

Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 73.91; H, 7.55; N, 3.31.

#### 5.18.4. (*E*,1*S*,4a*S*)-Methyl 1,2,3,4,4a,9,10,10a-octahydro-6-hydroxy-9-methoxyimino-1,4a-dimethylphenanthrene-1-carboxylate (6f)

A mixture of the methyl ester **6c** (98 mg, 0.285 mmol), pyridine (63 μL), and $NH_2OMe{\cdot}HCl$ (38 mg, 0.456 mmol) in EtOH (1 mL) was stirred at 100 °C overnight, then cooled, and evaporated in vacuo. The residue was purified by flash chromatography (*n*-hexane/AcOEt = 4:1) to afford **6f** (78 mg, 83% yield) as a light yellow solid. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.87 (d, $J$ = 8.6 Hz, 1H), 6.75 (d, $J$ = 2.5 Hz, 1H), 6.64 (dd, $J$ = 8.6, 2.5 Hz, 1H), 3.98 (s, 3H), 3.70 (s, 3H), 3.31 (dd of ABX system, $J$ = 18.8, 4.4 Hz, 1H), 2.98 (dd of ABX system, $J$ = 18.8, 13.8 Hz, 1H), 2.27–2.18 (m, 2H), 1.96 (m, 1H), 1.69–1.62 (m, 2H), 1.46 (td, $J$ = 13.3, 4.2 Hz, 1H), 1.28 (s, 3H), 1.08 (td, $J$ = 13.5, 3.8 Hz, 1H), 0.95 (s, 3H).

#### 5.18.5. (*E*,1*S*,4a*S*)-1,2,3,4,4a,9,10,10a-Octahydro-6-hydroxy-9-methoxyimino-1,4a-dimethylphenanthrene-1-carboxylic acid (7a)

Compound **6f** (25 mg, 0.075 mmol) was treated with $KOBu^t$ (1.13 mmol) in DMSO (1.13 mL) at 60 °C for about 2 h, then the reaction mixture was poured into ice-water, the whole was acidified with 2 N HCl, and extracted with AcOEt. The combined organic layer was washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and evaporated in vacuo. The crude mixture was purified by flash chromatography (*n*-hexane/AcOEt = 2:1) to afford **7a** (22 mg, 92% yield) as a colorless oil. $^1H$ NMR (Acetone-$d_6$, 400 MHz): $\delta$ 8.47 (br s, 1H), 7.82 (d, $J$ = 8.6 Hz, 1H), 6.83 (d, $J$ = 2.5 Hz, 1H), 6.67 (dd, $J$ = 8.6, 2.5 Hz, 1H), 3.90 (s, 3H), 3.29 (dd of ABX system, $J$ = 18.9, 4.5 Hz, 1H), 3.06 (dd of ABX system, $J$ = 18.9, 13.8 Hz, 1H), 2.30–2.21 (m, 2H), 2.11–1.96 (m, 1H), 1.69–1.60 (m, 2H), 1.49 (td, $J$ = 13.3, 4.1 Hz, 1H), 1.31 (s, 3H), 1.14 (td, $J$ = 13.4, 3.8 Hz, 1H), 1.05 (s, 3H). HR-MS: calcd for $C_{18}H_{23}NO_4$ ($[M+H]^+$), 318.1705; found, 318.1694.

Anal. Calcd for $C_{18}H_{23}NO_4{\cdot}3/4H_2O$: C, 65.34; H, 7.46; N, 4.23. Found: C, 65.56; H, 7.50; N, 4.15.

#### 5.18.6. (*E*,1*S*,4a*S*)-Methyl 6-(3-phenylpropoxy)-1,2,3,4,4a,9,10,10a-octahydro-9-methoxyimino-1,4a-dimethylphenanthrene-1-carboxylate (6j)

A solution of **6f** (24 mg, 0.072 mmol) and $Cs_2CO_3$ (35 mg, 0.108 mmol) in 1 mL DMF was stirred at r.t for 30 min, then 1-bromo-3-phenylpropane (14 μL, 0.094 mmol) was added. The mixture was stirred overnight at r.t, and poured into ice-water, then the whole was extracted with AcOEt 3 times. The combined organic layer was washed with water, and brine, and dried over $Na_2SO_4$. The crude mixture was purified by flash chromatography (*n*-hexane/AcOEt = 8:1) to afford **6j** (30 mg, colorless oil) in 92% yield. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.92 (d, $J$ = 8.7 Hz, 1H), 7.31–7.27 (m, 2H), 7.21 (m, 3H), 6.82 (d, $J$ = 2.5 Hz, 1H), 6.72 (dd, $J$ = 8.7, 2.5 Hz, 1H), 3.99 (s, 3H), 3.97 (t, $J$ = 6.3 Hz, 2H), 3.71 (s, 3H), 3.31 (dd of ABX system, $J$ = 18.7, 4.3 Hz, 1H), 2.97 (dd of ABX system, $J$ = 18.7, 13.8 Hz, 1H), 2.81 (t, $J$ = 7.3 Hz, 2H), 2.26 (m, 1H), 2.09 (m, 2H), 1.97 (m,1H), 1.71–1.64 (m, 2H), 1.53 (m, 1H), 1.29 (s, 3H), 1.09 (td, $J$ = 13.6, 3.8 Hz, 1H), 0.98 (s, 3H).

### 5.19. Synthesis of compounds 4b and 6k

Compound **6j** (183 mg, 0.407 mmol) was treated with $KOBu^t$ (684 mg, 6.1 mmol) in DMSO (6.00 mL) at 60 °C for about 2 h. The reaction mixture was poured into ice-water, acidified with 2 N HCl and extracted with AcOEt. The combined organic layer was washed with $H_2O$ and brine, dried over $Na_2SO_4$, filtered, and evaporated in vacuo. The crude mixture was purified by flash chromatography (*n*-hexane/AcOEt = 4:1) to afford **4b** (38 mg, 21% yield) and **6k** (65 mg, 35% yield) as yellow oil.

#### 5.19.1. (*E*,1*S*,4a*S*)-6-(3-Phenylpropoxy)-1,2,3,4,4a,9,10,10a-octahydro-9-methoxyimino-1,4a-dimethylphenanthrene-1-carboxylic acid (4b)

$^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.93 (d, $J$ = 8.7 Hz, 1H), 7.31–7.27 (m, 2H), 7.21 (m, 3H), 6.82 (d, $J$ = 2.5 Hz, 1H), 6.73 (dd, $J$ = 8.7, 2.5 Hz, 1H), 3.99 (s, 3H), 3.97 (t, $J$ = 6.4 Hz, 2H), 3.31 (dd of ABX system, $J$ = 18.8, 4.1 Hz, 1H), 3.05 (dd of ABX system, $J$ = 18.8, 13.9 Hz, 1H), 2.81 (t, $J$ = 7.3 Hz, 2H), 2.29–2.25 (m, 2H), 2.12 (m, 2H), 2.08 (m,1H), 1.74–1.67 (m, 2H), 1.52 (td, $J$ = 13.3, 3.7 Hz, 1H), 1.36 (s, 3H), 1.14 (td, $J$ = 13.6, 3.7 Hz, 1H), 1.08 (s, 3H). HR-MS: calcd for $C_{27}H_{33}NO_4$ ($[M+H]^+$), 436.2488; found, 436.2444.

Anal. Calcd for $C_{27}H_{33}NO_4{\cdot}1/4H_2O$: C, 73.69; H, 7.67; N, 3.18. Found: C, 73.79; H, 7.50; N, 3.17.

#### 5.19.2. (*E*,1*S*,4a*S*)-10-Hydroxy-6-(3-Phenylpropoxy)-1,2,3,4,4a,9,10,10a-octahydro-9-methoxyimino-1,4a-dimethylphenanthrene-1-carboxylic acid (6k)

$^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.70 (d, $J$ = 8.6 Hz, 1H), 7.29 (m, 2H), 7.21 (m, 3H), 6.83 (d, $J$ = 2.4 Hz, 1H), 6.76 (dd, $J$ = 8.6, 2.4 Hz, 1H), 6.05 (d, $J$ = 9.6 Hz, 1H), 4.07 (s, 3H), 3.98 (t, $J$ = 6.2 Hz, 2H), 2.81 (t, $J$ = 7.3 Hz, 1H), 2.28 (d, $J$ = 13.2 Hz, 1H), 2.19 (d, $J$ = 13.3 Hz, 1H), 2.11 (m, 2H), 1.97 (m,1H), 1.74–1.64 (m, 3H), 1.55 (s, 3H), 1.18 (td, $J$ = 13.5, 3.2 Hz, 1H), 0.99 (s, 3H). HR-MS: calcd for $C_{27}H_{33}NO_5$ ($[M+H]^+$), 452.2430; found, 452.2230.

Anal. Calcd for $C_{27}H_{33}NO_5$: C, 71.82; H, 7.37; N, 3.10. Found: C, 71.56; H, 7.36; N, 3.05.

#### 5.19.3. (*E*,1*S*,4a*S*,10a*R*)/-10-Hydroxy-9-((3-phenylpropoxy)imino) -6-(3-phenylpropoxy)-1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimeth ylphenanthrene-1-carboxylate (6i, same procedure as 4a)

Colorless oil. $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 7.69 (d, $J$ = 8.6 Hz, 1H), 7.31–7.27 (m, 4H), 7.21 (m, 6H), 6.82 (d, $J$ = 2.4 Hz, 1H), 6.76 (dd, $J$ = 8.6, 2.4 Hz, 1H), 6.09 (d, $J$ = 9.6 Hz, 1H), 4.27 (t, $J$ = 6.4 Hz, 2H), 3.98 (t, $J$ = 6.2 Hz, 2H), 2.81 (t, $J$ = 7.3 Hz, 2H), 2.75 (t, $J$ = 7.7 Hz, 2H), 2.25 (d, $J$ = 13.0 Hz, 1H), 2.18–2.05 (m, 5H), 1.93 (m, 1H), 1.69 (m, 3H), 1.53 (s, 3H), 1.17 (m, 1H), 0.98 (s, 3H). HR-MS: calcd for $C_{35}H_{41}NO_5$ ($[M+H]^+$), 578.2883; found, 578.2923.

### 5.20. General procedure for synthesis of compounds 4c–g

A mixture of **4a** (1 mmol), KOH (10 mmol), cat. NaI and an excess of the the corresponding alkyl bromide (5 mmol) in EtOH (2 mL) was refluxed overnight. The whole was cooled, and evaporated. The residue was diluted with water (10 mL), acidified with 2 N HCl, and extracted with AcOEt. The combined organic layer was washed with

brine, dried over $Na_2SO_4$, filtered, and evaporated in vacuo. The residue was purified by flash chromatography using *n*-hexane/ethyl acetate (4/1–2/1) as eluent to afford the desired compounds **4c**–**g**.

#### 5.20.1. (*E*,1*S*,4a*S*)-9-(Allyloxy)imino-6-(3-phenylpropoxy)-1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethylphenanthrene-1-carboxylic acid (4c)

Yellow oil, 98% conversion yield. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.93 (d, $J$ = 8.8 Hz, 1H), 7.29 (m, 2H), 7.21 (m, 3H), 6.82 (d, $J$ = 2.5 Hz, 1H), 6.72 (dd, $J$ = 8.8, 2.5 Hz, 1H), 6.15–6.05 (m, 1H), 5.35 (m, 1H), 5.23 (m, 1H), 4.70 (m, 2H), 3.97 (t, $J$ = 6.2 Hz, 2H), 3.37 (dd of ABX system, $J$ = 18.8, 4.3 Hz, 1H), 3.07 (dd of ABX system, $J$ = 18.7, 13.8 Hz, 1H), 2.81 (t, $J$ = 7.3 Hz, 2H), 2.28 (m, 2H), 2.10 (m, 2H), 2.05 (m,1H), 1.70 (m, 2H), 1.51 (m, 1H), 1.36 (s, 3H), 1.11 (m, 1H), 1.08 (s, 3H). HR-MS: calcd for $C_{29}H_{35}NO_4$ ([M+H]$^+$), 462.2644; found, 462.2678. Anal. Calcd for $C_{29}H_{35}NO_4$: C, 75.46; H, 7.64; N, 3.03. Found: C, 75.16; H, 7.64; N, 3.12.

#### 5.20.2. (*E*,1*S*,4a*S*)-9-((3-Methylbut-2-enyloxy)imino)-6-(3-phenylpropoxy)-1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl phenanthrene-1-carboxylic acid (4d)

Light yellow oil, 73% conversion yield. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.95 (d, $J$ = 8.7 Hz, 1H), 7.29 (m, 2H), 7.20 (m, 3H), 6.82 (d, $J$ = 2.4 Hz, 1H), 6.73 (dd, $J$ = 8.7, 2.4 Hz, 1H), 5.53 (t, $J$ = 6.9 Hz, 1H), 4.70 (d, $J$ = 6.9 Hz, 2H), 3.97 (t, $J$ = 6.3 Hz, 2H), 3.36 (dd of ABX system, $J$ = 18.7, 4.3 Hz, 1H), 3.04 (dd of ABX system, $J$ = 18.7, 13.9 Hz, 1H), 2.81 (t, $J$ = 7.3 Hz, 2H), 2.28 (m, 2H), 2.10 (m, 2H), 2.05 (m,1H), 1.79 (s, 3H), 1.76 (s, 3H), 1.69 (m, 2H), 1.51 (m, 1H), 1.36 (s, 3H), 1.10 (m, 1H), 1.08 (s, 3H). HR-MS: calcd for $C_{31}H_{39}NO_4$ ([M+H]$^+$), 490.2957; found, 490.2939.

#### 5.20.3. (*E*,1*S*,4a*S*)-9-((Prop-2-ynyloxy)imino)-6-(3-phenylpropoxy)-1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethylphenanthrene-1-carboxylic acid (4e)

Light yellow oil, 69% conversion yield. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.97 (d, $J$ = 8.8 Hz, 1H), 7.29 (m, 2H), 7.20 (m, 3H), 6.82 (d, $J$ = 2.5 Hz, 1H), 6.73 (dd, $J$ = 8.8, 2.5 Hz, 1H), 4.79 (d, $J$ = 2.4 Hz, 2H), 3.98 (t, $J$ = 6.4 Hz, 2H), 3.37 (dd of ABX system, $J$ = 18.8, 4.3 Hz, 1H), 3.08 (dd of ABX system, $J$ = 18.8, 13.9 Hz, 1H), 2.81 (t, $J$ = 7.3 Hz, 2H), 2.48 (t, $J$ = 2.4 Hz, 1H), 2.28 (m, 2H), 2.11 (m,2H), 2.00 (m, 1H), 1.70 (m, 2H), 1.51 (m, 1H), 1.37 (s, 3H), 1.11 (m, 1H), 1.09 (s, 3H). HR-MS: calcd for $C_{29}H_{33}NO_4$ ([M+H]$^+$), 460.2488; found, 460.2483.

Anal. Calcd for $C_{29}H_{33}NO_4$: C, 75.79; H, 7.24; N, 3.05. Found: C, 75.49; H, 7.23; N, 2.98.

#### 5.20.4. (*E*,1*S*,4a*S*)-9-(Benzyloxy)imino-6-(3-phenylpropoxy)-1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethylphenanthrene-1-carboxylic acid (4f)

Yellow oil, 92% conversion yield. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.93 (d, $J$ = 8.8 Hz, 1H), 7.45 (m, 2H), 7.37 (m, 2H), 7.29 (m, 3H), 7.20 (m, 3H), 6.82 (d, $J$ = 2.5 Hz, 1H), 6.72 (dd, $J$ = 8.8, 2.5 Hz, 1H), 5.24 (s, 2H), 3.97 (t, $J$ = 6.3 Hz, 2H), 3.41 (dd of ABX system, $J$ = 18.7, 4.3 Hz, 1H), 3.09 (dd of ABX system, $J$ = 18.7, 13.8 Hz, 1H), 2.81 (t, $J$ = 7.3 Hz, 2H), 2.28 (t, $J$ = 13.4 Hz, 2H), 2.10 (m, 2H), 2.04 (m, 1H), 1.70 (m, 2H), 1.51 (m, 1H), 1.36 (s, 3H), 1.11 (m, 1H), 1.08 (s, 3H). HR-MS: calcd for $C_{33}H_{37}NO_4$ ([M+H]$^+$), 512.2801; found, 512.2771.

Anal. Calcd for $C_{33}H_{37}NO_4$: C, 77.47; H, 7.29; N, 2.74. Found: C, 77.19; H, 7.24; N, 2.64.

#### 5.20.5. (*E*,1*S*,4a*S*)-9-((3-Phenylpropoxy)imino)-6-(3-phenyl propoxy)-1,2,3,4,4a,9,10,10a-octahydro-1,4a-dimethyl phenanthrene-1-carboxylic acid (4g)

Light yellow oil, 61% conversion yield. $^1$H NMR ($CDCl_3$, 400 MHz): $\delta$ 7.93 (d, $J$ = 8.8 Hz, 1H), 7.29 (m, 4H), 7.22 (m, 6H), 6.82 (d, $J$ = 2.4 Hz, 1H), 6.72 (dd, $J$ = 8.8, 2.4 Hz, 1H), 4.21 (t, $J$ = 6.5 Hz, 2H), 3.97 (t, $J$ = 6.3 Hz, 2H), 3.37 (dd of ABX system, $J$ = 18.7, 4.3 Hz, 1H), 3.06 (dd of ABX system, $J$ = 18.7, 13.9 Hz, 1H), 2.81 (t, $J$ = 7.4 Hz, 2H), 2.75 (t, $J$ = 7.4 Hz, 2H), 2.27 (m, 2H), 2.11 (m, 6H), 2.06 (m, 1H), 1.71 (m, 2H), 1.51 (m, 1H), 1.36 (s, 3H), 1.11 (m, 1H), 1.08 (s, 3H). HR-MS: calcd for $C_{35}H_{41}NO_4$ ([M+H]$^+$), 540.3114; found, 540.3071.

### 5.21. Biological assay

Effects of compounds on hBK currents were evaluated in CHO cells stably expressing hBK$\alpha$ channel by population patch clamp methods with automated patch clamp system, Ion Works™ Quatro (Molecular devices, Inc., Sunnyvale, CA). Composition of internal solution was (in mM) 140 KCl, 1.0 $MgCl_2/6H_2O$, 20 HEPES (pH 7.25–7.3 with KOH). And extracellular solution used was (in mM) 137 NaCl, 4.0 KCl, 1.0 $MgCl_2/6H_2O$, 2.0 $CaCl_2$, 10 glucose, 20 HEPES (pH 7.4 with NaOH). Cells were suspended in extracellular solution containing 20 μM BAPTA-AM just prior loading to the cell boat in IonWorks. The internal solution was substituted to that containing amphotericin B (25 mg/mL) to establish the perforated patch clamp mode. Cells were voltage clamped at a holding potential of −90 mV and the currents were elicited by a step pulse to +100 mV pulse (350 msec) followed by a ramp pulse from −90 mV to 100 mV (1650 msec). The external solution contained 1 μM ionomycin to activate hBK current. The currents elicited by a step pulse to 100 mV before and after the application of test compounds (30 μM) were used to evaluate the current activation by compounds. The effects of compounds were shown by the % of pre-value. The data of each compound represent the average of 8 wells.

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