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Synthesis of two marine farnesylacetones that dilate the basilar arteries of rabbits

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ABSTRACT

We have synthesized novel vasodilatation farnesylacetones **1** and **2,** which are major active constituents of *Sargassum siliquastrum* collected from the coast of the East Sea in Korea, in 9 steps. A test of the vasodilatation effect of synthetic intermediates and their deprotected compounds on the basilar arteries of rabbits revealed that **14** and **14-1** have a similar dilation effect as their target marine natural products **1** and **2**.

Although terrestrial plants and microorganisms are important sources of clinical drugs,[1] researchers have recently begun focusing on marine resources for drug discovery because of their considerable biodiversity in oceans, which cover over 70% of Earth.[1] Various marine natural products have been found to be useful in physiological and pharmacological studies,[2] and many researchers have performed clinical trials or preclinical evaluations for cancer,[3–5] pain,[6,7] inflammation,[8,9] and Alzheimer's dementia[10] using them.

Because vascular-related diseases such as hypertension, stroke, subarachnoid hemorrhage, and Alzheimer's dementia are a threat to public health, developing modulators that control vascular tone and alleviate the symptoms of these conditions is an urgent need.[11,12] We are a part of the marine biology program at the Center for Marine Drug Discovery, and we were the first to report that sargahydroquinoic acid extracted from the brown algae *Sargassum micracanthum* selectively dilates the basilar artery of white rabbits to more than 10-fold the diameter of the carotid artery.[13] After that, we reported the discovery of farnesylacetones (**1** and **2**) in Figure 1, which were isolated from *Sargassum siliquastrum*, that dilate the basilar and carotid arteries of rabbits.[14] These farnesylacetones are promising candidates for antihypertensive drugs because they dilate blood vessels such as the basilar and carotid arteries.[14] Compound **2** and its related compounds, except **1,** were isolated from the brown algae *S. micracanthum* in 1979,[15] and farnesylacetones **1** and **2** were also discovered by another group in 1982.[16] Before our report about their vasodilatation activity, it was reported that they and their related natural products inhibit cholinesterase.[17,18] As previously reported, the biological properties of our target farnesylaceones **1** and **2** are well studied, but despite their biological importance, their total synthesis remained to be achieved.

As reported in our previous Letter,[14] low yields of farnesylaceones **1** and **2** are obtained when they are extracted and purified from the marine natural source. Therefore, we decided to synthesize the farnesylaceones efficiently for the further studies, which included in vivo and toxicity tests. Their isolation yields from the dried crude extract obtained after several HPLC preparations were just 0.6% for **1** and 1% for **2**.[14]

In this Letter, we describe an efficient method for synthesizing farnesylacetones **1** and **2** and describe the vasodilatation effect of their synthetic intermediates. The established synthesis route for these target lead compounds was used to synthesize a library of chemical mimics in order to discover potential antihypertensive agents.

In order to efficiently synthesize novel vasodilatation marine natural products, we attempted the retrosynthetic analysis shown in Scheme 1. Adding the C-11 carbanion to isovaleraldehyde in route A appears to be more efficient than the isobutyl anion reaction with a C-12 linear aldehyde.

As shown in Scheme 2, our first attempt at forming C-15 linear chain **8**, an important intermediate for our target molecules (**1** and **2**), started with the allylic hydroxylation of the commercially available geranyl acetone **3** with selenium dioxide and *t*-butyl

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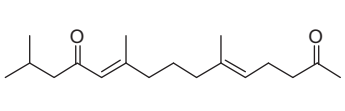
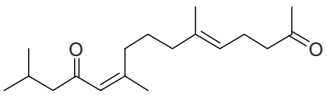


(5*E*,10*E*)-6,10,14-trimethylpentadeca-5,10-diene-2,12-dione(**1**)

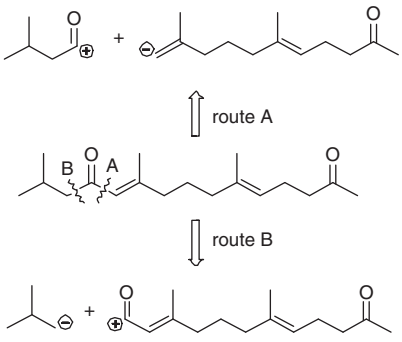
EC_{50} for Basilar artery 1.22μM
for Carotid artery 13.7μM



(5*E*,10*Z*)-6,10,14-trimethylpentadeca-5,10-diene-2,12-dione(**2**)

EC_{50} for Basilar artery 3.72μM
for Carotidartery 14.5μM

Figure 1. 10*E*-Farnesylacetone (**1**) and 10*Z*-farnesylacetone (**2**) purified from *Sargassum siliquastrum* by activity-guided separation.



Scheme 1. Retrosynthesis of 10*E*-Farnesylacetone (**1**).

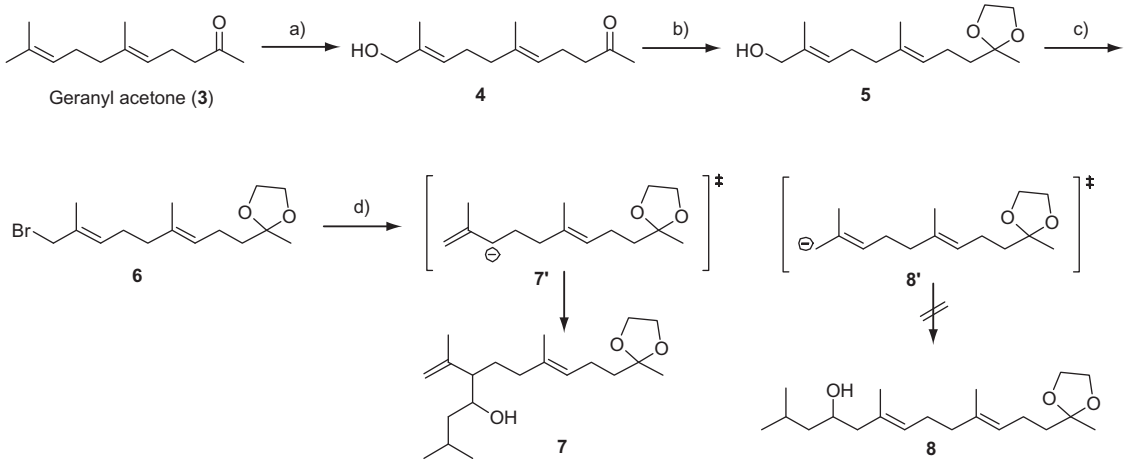
Table 1
Vasodilation potency of synthetic and deprotected intermediates after depolarization-induced constriction of the basilar artery of rabbit

	Effective percentage (%) at 10 μM
10	13.1 ± 3.8[a]
11	33.5 ± 4.2
12	44.6 ± 7.2
12-1	10.3 ± 3.4
13	20.1 ± 4.3
13-1	12.6 ± 3.5
14	99.8 ± 0.2
14-1	98.9 ± 1.1
15	83.3 ± 7.2

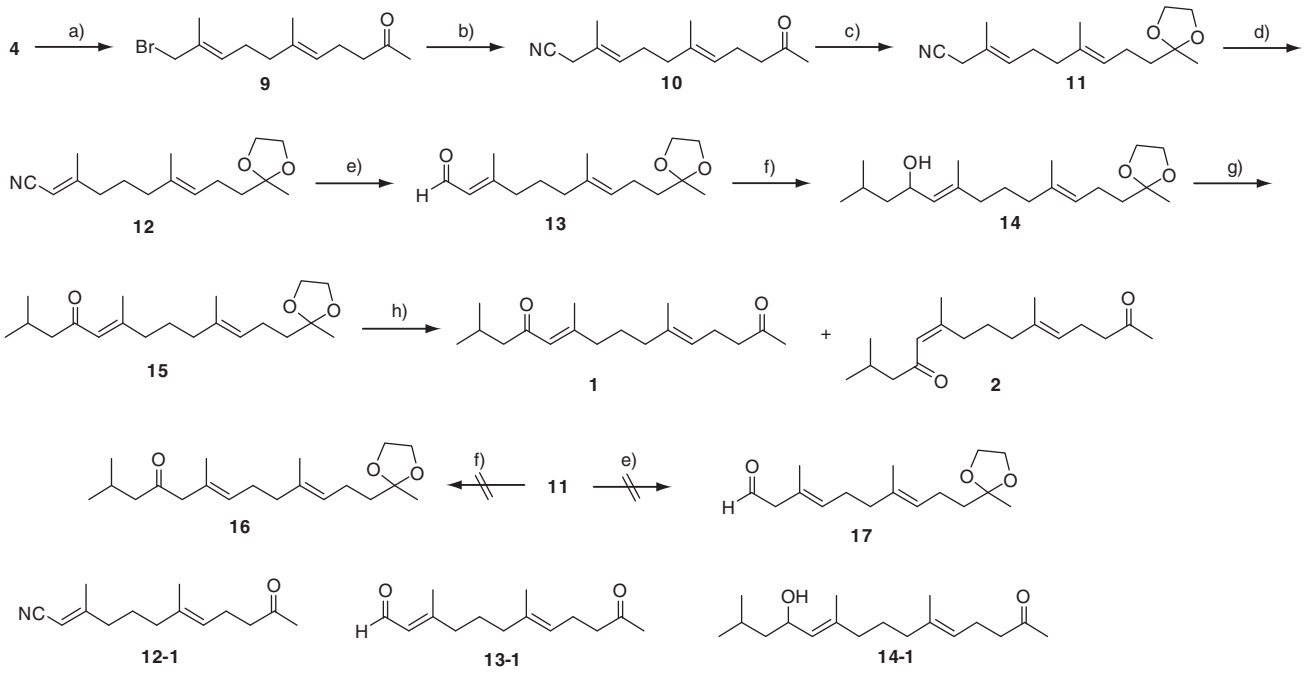
[a] Values are means of four experiments.

hydroperoxide in dichloromethane to yield an allylic alcohol **4**.[19] Compound **4** was protected with ethylene glycol in toluene and *p*-toluene sulfonic acid to yield known protected compound **5**.[20] The addition of methanesulfonyl chloride, followed by the addition of lithium bromide to **5** in tetrahydrofuran at −40 °C yielded bromo allylic molecules **6** (75% yield). In order to obtain synthetic intermediate **8**, we needed to regioselectively generate a terminal allylic organometallic reagent. However, in Barbier type reactions of non-symmetrical linear allylic chains, using magnesium, tin, zinc, indium, and other metals, the more favorable structure was the rearranged compound **7′** not **8′**.[21] Although we tried to obtain linear intermediate **8** using a report that described a method for obtaining a terminal allylic anion using Sn in a similar system,[22] we only acquired branched compound **7**, whose presence was confirmed by the presence of a terminal methylene proton peak of 4.9 and 4.7 ppm in the ^{1}H NMR data. The Umpolung approach can also be used to obtain **8** from isovaleraldehyde,[23,24] but this approach did not work in our system.

Since compound **7** had a moderate vasodilatation effect (data not shown in this Letter), we tried to synthesize our target molecule via route B. As shown in Scheme 1, the key reaction is the addition of an isobutyl anion to the α,β-unsaturated aldehyde **13**. Keto bromide **9** is obtained from compound **4** through the same reaction as the one that yields protected bromide **6**. Cyanation of **9** with sodium cyanide in DMF and acetonitrile solution and the successive protection of the ketone moiety with ethylene glycol afforded a nitrile compound **11**. In this stage, if a carbanion can be added to **11**, precursor **16** of the target compound can be obtained. However, we could not obtain **16** via a Grignard reaction with **11** and isobutylmagnesium bromide.[25] Therefore, in order to transform the cyano group to a more reactive aldehyde moiety, we reduced **11** with DIBAL-H in methylene chloride to obtain aldehyde **17**, which could react with its corresponding Grignard reagent to efficiently afford our target compounds (**1** and **2**). However, this reduction also failed because it appears that the acidic α proton reacts with the hydride of DIBAL-H. Fortunately,



Scheme 2. Reagents and conditions: (a) SeO_2 (0.2 equiv), *t*-BuOOH (2.0 equiv), CH_2Cl_2, r, 30 min, 48%; (b) ethylene glycol (8.0 equiv), *p*-TsOH (0.6 equiv), toluene, reflux, 12 h, 95%; (c) methanesulfonyl chloride (2.0 equiv), NEt_3 (1.6 equiv), CH_2Cl_2, −40 °C, 30 min and then LiBr (2.5 equiv), CH_2Cl_2, −40 °C to rt, 4 h, 75%; (d) isovaleraldehyde (3.3 equiv), Zn (−3.0 equiv), THF, reflux, 2 h, 89%.



Scheme 3. Reagents and conditions: (a) methanesulfonyl chloride (2.0 equiv), NEt_3 (1.6 equiv), CH_2Cl_2, −50 °C, 4 h and then LiBr (2.5 equiv), CH_2Cl_2, −40 °C to rt, 1 h, 62%; (b) NaCN (3 equiv), DMF:CH_3CN(1:1), rt, 4 h, 93%; (c) ethylene glycol (8.0 equiv), *p*-TsOH (0.6 equiv), benzene, reflux, 5 h, 56%; (d) $NaOCH_3$(2.0 equiv), MeOH, reflux, 6 h, 87%; (e) DIBAL-H (2.5 equiv), MC, −40 °C, 79%; (f) isobutyl magnesium bromide (3.0 equiv), THF, rt, 2 h, 85% (g) PCC (1.6 equiv), MC, rt, 66%; (h) PPTS (1.0 equiv), acetone:H_2O(8:2), reflux, 3 h, 67%.

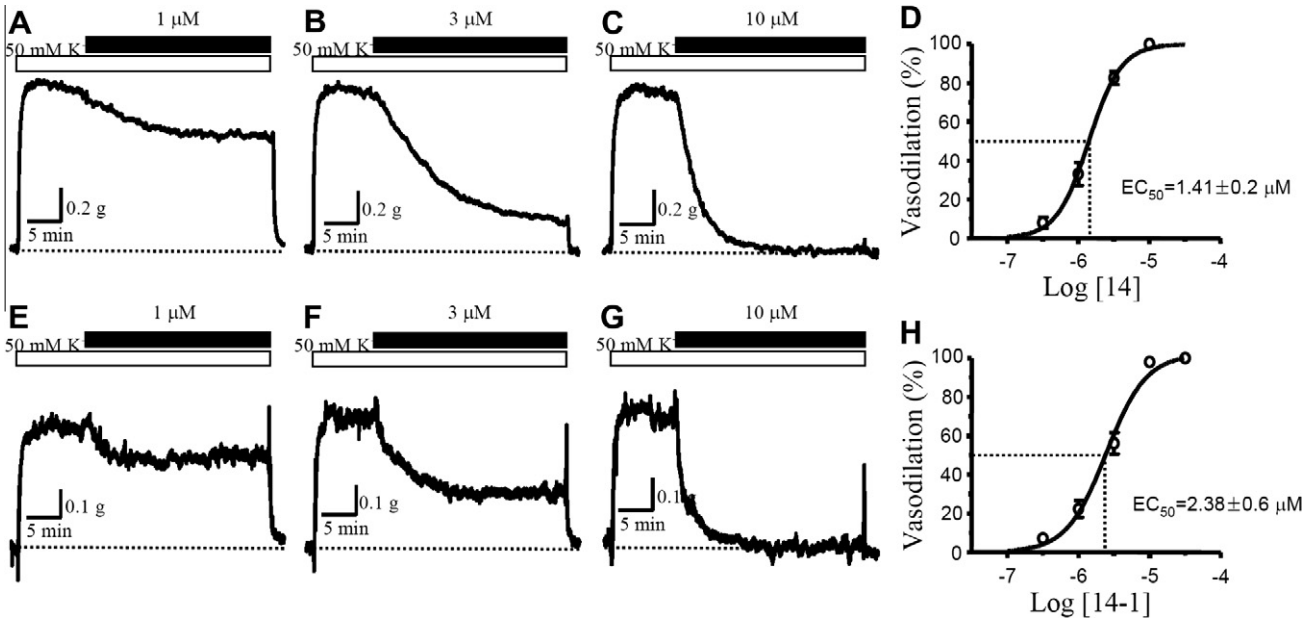


Figure 2. Vasodilatative effects of synthetic intermediates **14** and **14-1** on depolarization-induced vasoconstriction of rabbit basilar artery.

conjugate nitrile **12** was obtained because of the double bond migration of **11** with sodium methoxide in methanol, and the reduction of **12** with DIBAL-H yielded α,β-unsaturated aldehyde **13**, which reacts with isobutylmagnesium bromide to give **14**. After PCC oxidation of **14**, followed by successive deprotection with PPTS in acetone and water solution, we obtained novel vasodilatative marine natural products **1** and **2** (Scheme 3). The two compounds have spectral data identical to those of their respective purified natural products.[26]

We have already reported the vasodilatation effect of **1** and **2**, and so, we tested the vasodilatation effects of the synthetic intermediates formed via Scheme 2 in an organ bath system.[27] First, we wanted to examine whether the synthetic intermediates and some deprotected intermediates (**12-1**, **13-1**, and **14-1**) dilated the basilar arteries of white rabbits. We tested the vasodilatation potency of our candidate compounds at a single concentration of 10 μM; the results are summarized in Table 1. The tested compounds were divided into two groups based on their potency and

chain structure. One group included 12-carbon chain compounds (**10**–**13-1**) that had a weak vasodilatation effect, while the other group comprised 15-carbon chain compounds (**14**–**15**) that had a potent dilation effect on the basilar vessels; the compounds in the second group had potencies similar to those of the lead compounds (**1** and **2**). In addition, the preliminary structure–activity relationship presented in Table 1 suggests that the isobutyl moiety is critical for the vasodilatation effect. In order to obtain more potent drug candidates, the isobutyl group needs to be replaced by a group with more versatile functionality. In our lab, it is undergoing to get chemical library from proper structure derivatization.

As illustrated in Figure 2, a single application of **14** in log scale concentration induced vasodilatation of the basilar artery, causing it to contract in a salt solution containing a high concentration of K^+ (50 mM K^+). Likewise, **14-1** also induced concentration-dependent vasodilatation of the basilar artery. The concentration-response line was created by curve fitting, using the Hill equation $[E = (1 + EC_{50}/[\mathbf{14} \text{ or } \mathbf{14\text{-}1}]^n)^{-1}]$ and revealed that the concentrations of **14** and **14-1** at half maximal vasodilatation (EC_{50}) were 1.41 ± 0.2 and 2.38 ± 0.6 μM (n = 5), respectively, for the basilar artery. The EC_{50} values of **1** and **2** are 1.22 and 3.72 μM, respectively; thus, **14** and **14-1** have almost the same potency as **1** and **2**.

In conclusion, we completely synthesized novel vasodilatation marine natural farnesylacetones **1** and **2** from geranyl acetone through a 9-step reaction. When the dilation effect of the synthetic intermediates on the basilar artery of white rabbit was tested, compounds **14** and **14-1** had potency comparable to that of their target compounds **1** and **2**. Hence, we conclude that the terminal isobutyl moiety with a hydrophobic character is critical for dilatation of the basilar artery. We intend to replace the isobutyl group with a group with diverse functionality showing more hydrophobic property and develop novel antihypertensive agents, using the method we developed for synthesizing target molecules **1** and **2**.

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26. *Spectral data for* **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.55 (1H, m), 5.07 (1H, m), 3.97 (2H, s), 2.46 (2H, m), 2.25 (2H, m), 2.13 (3H, s), 2.10 (2H, m), 2.01 (2H, m), 1.74 (3H, s), 1.61 (3H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 135.6, 132.2, 131.0, 123.2, 43.8, 41.8, 41.7, 38.6, 29.9, 26.6, 22.4, 14.6 ppm; **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (1H, m), 5.09 (1H, m), 3.02 (2H, s), 2.47 (2H, m), 2.27 (2H, m), 2.13 (3H, m), 2.04 (2H, s), 2.01 (2H, s), 1.73 (3H, s), 1.61 (3H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.7, 135.5, 129.4, 124.1, 123.3, 117.8, 43.7, 38.8, 31.1, 30.0, 26.3, 22.2, 16.0, 15.9 ppm; **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.45 (1H, m), 5.14 (1H, m), 3.95 (4H, m), 3.02 (2H, s), 2.04 (2H, m), 2.01 (2H, m), 1.98 (2H, m), 1.72 (3H, s), 1.61 (3H, s), 1.57 (2H, m), 1.48 (3H, m) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.4, 129.5, 125.5, 124.3, 117.7, 110.1, 64.7, 64.6, 39.3, 31.1, 27.2, 26.5, 23.8, 23.3, 22.6, 15.9 ppm; **12**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.12 (2H, m), 3.95 (4H, m), 2.18–1.94 (6H, m), 2.04 (2H, m), 1.69–1.50 (4H, m), 1.59 (3H, s), 1.33 (3H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 134.1, 134.0, 125.7, 125.1, 109.9, 95.1, 64.7, 39.0, 38.7, 37.9, 30.9, 25.1, 23.8, 22.6, 20.9, 15.7 ppm; **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.0 (1H, d, J = 9.0 Hz) 5.87 (1H, d, J = 9.0 Hz) 5.14 (1H, m), 3.94 (4H, m), 2.25–1.97 (8H, m), 1.69–1.50 (4H, m), 1.59 (3H, s), 1.33 (3H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.2, 164.2, 134.2, 127.3, 124.9, 109.8, 64.6, 40.0, 38.9, 31.3, 25.3, 23.8, 22.6, 17.5, 15.7 ppm; **13-1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.0 (1H, d, J = 9.0 Hz) 5.90 (1H, d, J = 9.0 Hz) 5.10 (1H, d, J = 9.0 Hz), 2.50 (2H, m), 2.25–1.97 (8H, m), 2.17 (3H, s), 1.67 (3H, s), 1.61 (3H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.3, 135.5, 127.3, 124.1, 123.4, 43.6, 40.0, 31.1, 29.9, 25.3, 23.1, 22.3, 17.5, 15.7 ppm; **14**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.16 (2H, m), 4.43 (1H, m), 3.95 (4H, m), 2.17 (2H, s), 2.12–1.91 (6H, m), 1.72–1.45 (5H, m), 1.59 (3H, s), 1.32 (3H, s), 1.25 (2H, m), 0.92 (6H, t, J = 6.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 135.4, 129.1, 128.5, 124.2, 66.4, 64.6, 46.9, 39.4, 39.1, 31.8, 31.1, 26.6, 26.0, 24.7, 23.8, 23.1, 22.6, 15.8 ppm; **14-1**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.56 (1H, d, J = 15.0 Hz), 5.16 (1H, t, J = 9.0 Hz), 2.43 (1H, m), 2.13 (3H, s), 2.12–1.91 (6H, m), 1.72–1.45 (6H, m), 1.27(6H, s), 0.88 (6H, t, J = 6.0 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 136.5, 126.6, 123.4, 72.8, 43.9, 42.4, 41.6, 39.8, 31.8, 31.0, 29.9, 28.3, 28.1, 23.2, 22.2, 15.8 ppm; **15**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (1H, s), 5.14 (1H, t, J = 6.0 Hz), 3.94 (4H, m), 2.25–1.94 (11H, m), 1.67–1.53 (4H, m), 1.33 (3H, s), 1.32 (3H, s), 0.93 (3H, s), 0.92 (3H, s) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.2, 158.3, 134.5, 124.6, 123.5, 109.8, 64.6, 53.4, 40.6, 39.0, 31.2, 25.6, 25.1, 23.7, 22.6, 19.2, 15.7 ppm.
27. *Test for vasodilatation effect*: After anesthetizing 12 male white rabbits, weighing 2–2.5 kg, by enflurane inhalation, the basilar and common carotid arteries were isolated rapidly under sterile conditions and placed in physiological salt solution (PSS) containing 137 mM NaCl, 5.4 mM KCl, 1.5 mM $CaCl_2$, 1 mM $MgCl_2$, 23.8 mM $NaHCO_3$, and 5.5 mM glucose. Residual blood was rinsed from the lumen, and adherent connective tissue, fat, and adventitia were carefully removed. The basilar and carotid arteries were cut into rings (3 mm) in a dissecting chamber filled with PSS and saturated with a mixture of 95% O_2 and 5% CO_2. The basilar and carotid rings were mounted using a pair of stainless steel hooks under a resting tension of 0.6 g and 1.5 g, respectively, in organ baths containing 15 mL PSS, which was maintained at 37 °C and through which a mixture of 95% O_2 and 5% CO_2 was bubbled. One of the hooks was connected to a force displacement transducer (MLT050; AD Instruments, Colorado Springs, CO), and the tension was recorded with Powerlab/400 on a chart program (AD Instruments). After equilibration for 30 min, each ring specimen was repeatedly exposed to a high concentration K^+ solution (50 mM K^+), which was prepared by replacing NaCl with an equimolar concentration of KCl, until the responses stabilized. Functionality of the endothelial cells was confirmed by the ability of acetylcholine (10 μM) to induce relaxation. Concentration–response relationships were obtained by a single application of synthetic intermediates in log scale concentration after the precontraction of the basilar and common carotid arteries, induced by exposure to a high concentration of K^+, reached a steady state.