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Synthesis of VS-105: A novel and potent vitamin D receptor agonist with reduced hypercalcemic effects ☆

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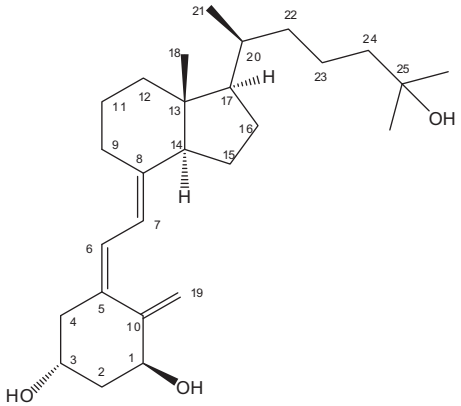
ABSTRACT

We have synthesized a novel vitamin D receptor agonist VS-105 ((1*R*,3*R*)-5-((*E*)-2-((3α*S*,7α*S*)-1-((*R*)-1-((*S*)-3-hydroxy-2,3-dimethylbutoxy)ethyl)-7α-methyldihydro-1*H*-inden-4(2*H*,5*H*,6*H*,7*H*,7α*H*)-ylidene) ethylidene)-2-methylenecyclohexane-1,3-diol). Preparation of a-ring phenylphosphine oxide **11**, followed by Wittig–Horner coupling of **11** with the protected 25-hydroxy Grundmann's ketone **22** generated the precursor **12**. Deprotection of the TBDMS groups of **12** produced the target compound VS-105. The biological profiles of VS-105 were evaluated using in vitro assays (VDR receptor binding, VDR reporter gene and HL-60 differentiation) in comparison to calcitriol (the endogenous hormone) or paricalcitol. Furthermore, the PTH suppressing potency and hypercalcemic side effects of VS-105 were evaluated in the 5/6 nephrectomized uremic rats in comparison to paricalcitol. Combining various changes at 20-epi, 22-oxa, 24-methyl, and 2-methylene yielded VS-105 that not only is highly potent in inducing functional responses in vitro, but also effectively suppresses PTH in a dose range that does not affect serum calcium in the 5/6 nephrectomized uremic rats.

The synthesis of vitamin D_3 occurs in the skin, but vitamin D_3 is not active and needs to be converted to 25-hydroxyvitamin D_3 ($25(OH)D_3$) and then further hydroxylated (by CYP27B1) to form the active hormone, calcitriol ($1,25(OH)_2D_3$). Calcitriol, the active bolite of vitamin D, is a secosteroid hormone that, by activating the vitamin D receptor (VDR), regulates multiple signaling pathways in various cells and tissues.[1,2] Numerous epidemiological and bench science studies demonstrate that activated VDR is involved in regulating many genes and functions including PTH, endothelial function, the cardiovascular, CNS, immune, and renal systems.[3–7]

During the past three decades, a majority of the studies in the VDR field have focused on elucidating its role in mineral homeostasis such as regulation of parathyroid hormone (PTH), intestinal calcium and phosphate absorption and bone metabolism.[2] Consequently, it is now well recognized that vitamin D deficiency results in defective intestinal absorption of calcium and phosphate and skeletal disorders. Furthermore, calcitriol (the endogenous VDR modulator, VDRM) and its analogs such as paricalcitol and doxercalciferol have been developed to treat hyperparathyroidism secondary to chronic kidney disease,[8] osteoporosis[9] and psoriasis.[10]

Despite encouraging data on VDRM's benefits for the cardiovascular, immune, and renal systems, currently VDRM is mainly indicated for managing secondary hyperparathyroidism (SHPT) in CKD,[11,12] and to a lesser degree used to treat osteoporosis and psoriasis.[13,14] The reason for this is due to factors including the narrow



20-epi-calcitriol

Figure 1. The structure of 20-epi-calcitriol.

Abbreviations: Ca, calcium; CKD, chronic kidney disease; NX, nephrectomized; PTH, parathyroid hormone; Pi, phosphate; VDR, vitamin D receptor; VDRMs, VDR modulators.

☆ The results presented in this Letter have not been published previously in whole or part, except in abstract format.

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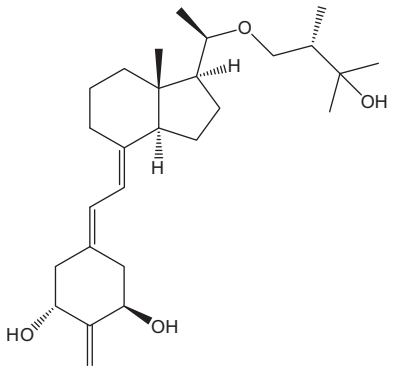

Figure 2. The structure of VS-105 ((1*R*,3*R*)-5-((*E*)-2-((3α*S*,7α*S*)-1-((*R*)-1-((*S*)-3-hydroxy-2,3-dimethylbutoxy)ethyl)-7α-methyldihydro-1*H*-inden-4(2*H*,5*H*,6*H*,7*H*,7α*H*)-ylidene)ethylidene)-2-methylenecyclohexane-1,3-diol).

therapeutic window of current VDRMs in the one to fourfold range as determined by comparing doses required for efficacy versus the hypercalcemic toxicity. Calcium is important to many body functions and calcium homeostasis is tightly regulated by various mechanisms including PTH and calcitriol. Hypercalcemia (too much serum calcium) interferes with numerous physiological functions. In severe cases hypercalcemia can lead to death. Thus, hypercalcemia is a serious concern for current VDRMs. Numerous VDRMs have been made with the intention to curtail their hypercalcemic side effect so that they can be developed for indications beyond their current usages.[15] However, very little knowledge is available regarding the SAR for VDRMs.

A review of the published papers on VDRMs reveals some interesting observations: (1) 20-epi-calcitriol (Fig. 1) is significantly more potent than calcitriol likely because the 20*S* configuration improves the recruiting of specific cofactors to the VDR transcriptional complex.[16–19] (2) Transposing the methylene group from C-10 to C-2 on the A-ring did not significantly alter the activity of the

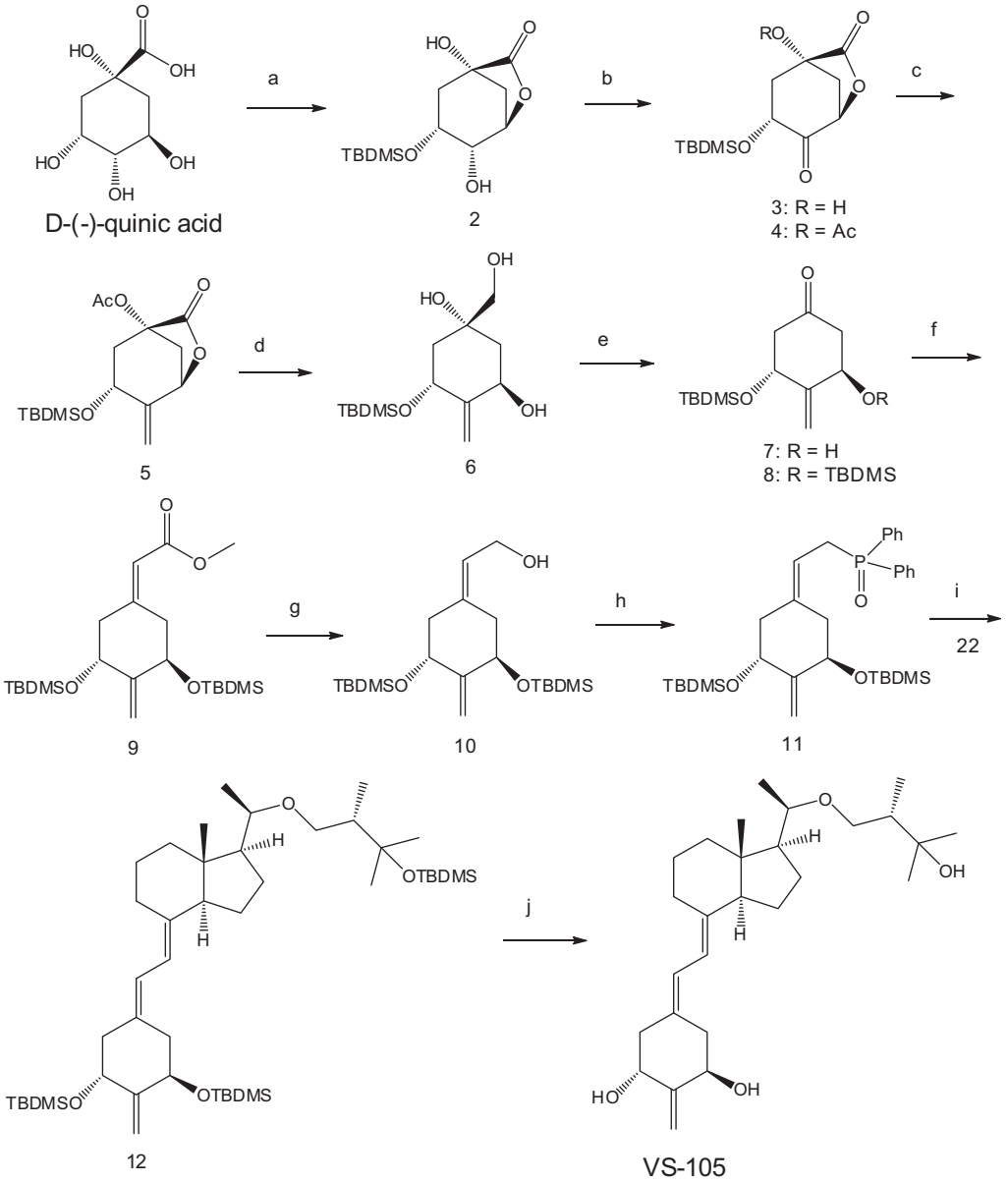

Figure 3. Synthetic scheme of VS-105. Reagents and conditions: (a) *p*-TosOH, toluene, TBDMS-Cl; (b) Dess–Martin periodinane, CH_2Cl_2 (93.2%); Ac_2O, pyridine (85.1%); (c) Ph_3PCH_3Br, THF, *n*-BuLi, 0 °C (30.7%); (d) $NaBH_4$, EtOH, 0 °C (50.6%); (e) $NaIO_4$, MeOH, 0 °C (93.7%); 2,6-lutidine, TBDMSOTf, −50 °C (46.6%); (f) LDA, THF, $(CH_3)_3SiCH_2CO_2CH_3$, −78 °C (69.6%); (g) DIBAL-H, toluene, −78 °C (85.9%); (h) *n*-BuLi, THF, TsCl, 0 °C; Ph_2PH, *n*-Buli, 0 °C; 10% H_2O_2, 0 °C (78.5%); (i) *n*-BuLi, THF, −78 °C (37.6%); (j) *n*-Bu_4NF, THF (59.7%).

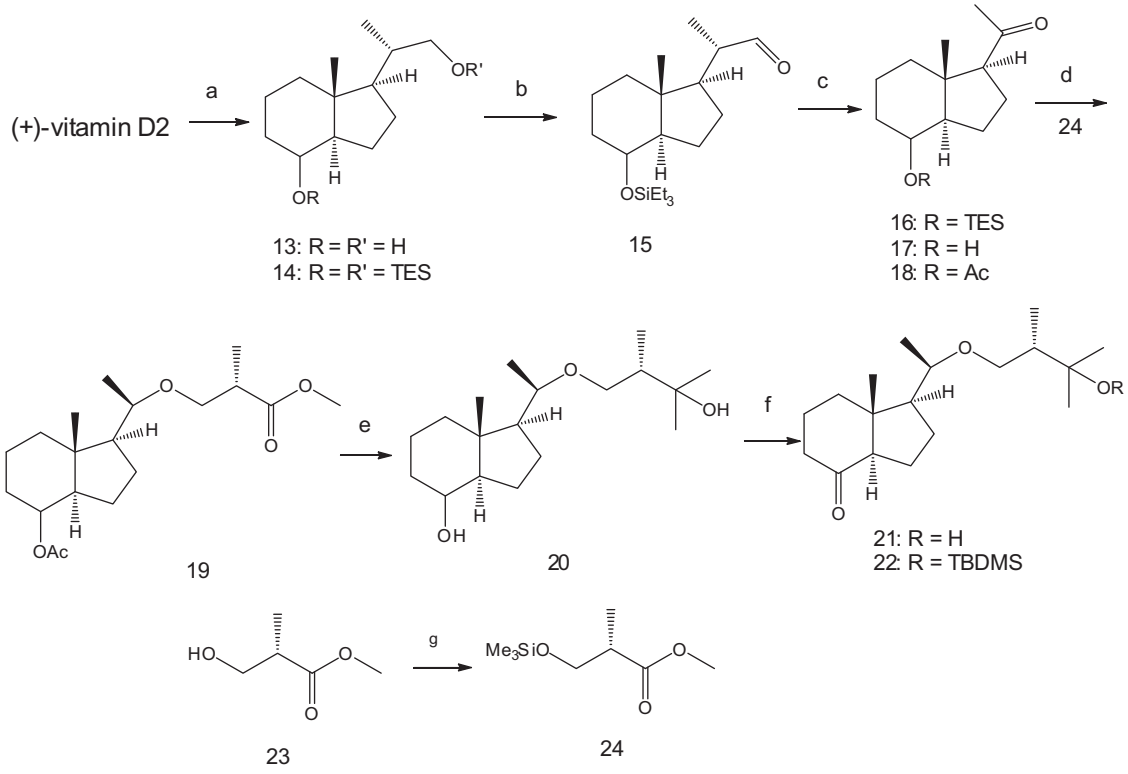

Figure 4. Synthetic scheme of the protected 25-hydroxy Grundmann's ketone **22**. Reagents and conditions: (a) Ozone, CH_2Cl_2/MeOH, $NaBH_4$, −78 °C (75%); 2,6-lutidine, TESOTf, THF, −78 °C (80%); (b) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N, −60 °C (80%); (c) morpholine, toluene, CuCl, O_2, CH_3CN (38.7%); *n*-Bu_4NF, THF (99%); Ac_2O, DMAP, pyridine, CH_2Cl_2, 0 °C (93.3%); (d) 24, TESOTf, CH_2Cl_2, −78 °C, Et_3SiH (45.9%); (e) CH_3MgBr, THF (98.3%); (f) Dess–Martin periodinane, CH_2Cl_2 (69.5%); 2,6-lutidine, TBDMSOTf, −50 °C (63.4%); (g) TMSCl, TEA, CH_2Cl_2, (65.1%).

Table 1
The potency of VS-105 was evaluated in three different in vitro assays in comparison to calcitriol or paricalcitol

	Ligand	IC_{50}/EC_{50}, (nM)
VDR receptor binding	VS-105	38
	Calcitriol	9.3
VDR reporter gene	VS-105	<0.1
	Calcitriol	15
HL-60 differentiation	VS-105	11.8
	Calcitriol	17.9
	Paricalcitol	12.5

Note: The methods for evaluating the in vitro potency of VDRMs in VDR receptor binding, VDR reporter gene and HL-60 differentiation assays have been published previously.[32–34]

compound.[20] (3) A combination of 20S configuration and transposing the methylene group from C-10 to C-2 on the A-ring significantly increases the compound's activity in inducing HL-60 differentiation and also in promoting intestinal calcium transport and increase calcium mobilization from the bone.[21–23] (4) One single change in the calcitriol structure from the carbon atom at the C-22 position to an oxygen atom reduces VDR binding activity and also reduces the hypercalcemic potential likely due to different cofactor recruitment.[24–27] (5) Adding an epi-methyl group to the C-24 position of calcitriol enhances the activity.[28]

We raised the question: will combining the changes at 20-epi, 22-oxa, 24-methyl, and 2-methylene affect the potency and the hypercalcemic potential of a VDRM? We therefore prepared a compound VS-105 ((1*R*,3*R*)-5-((*E*)-2-((3α*S*,7α*S*)-1-((*R*)-1-((*S*)-3-hydroxy-2,3-dimethylbutoxy)ethyl)-7α-methyldihydro-1*H*-inden-4(2*H*,5*H*,6*H*,7*H*,7α*H*)-ylidene)ethylidene)-2-methylenecyclohexane-1,3-diol) as shown in Figure 2 and determined its potency and hypercalcemic effect using in vitro and in vivo approaches.

The synthetic scheme of Vida-105 is outlined in Figure 3. According to the method described in the literature,[30] (−)-quinic acid was gently refluxed in toluene for 12 h in the presence of *p*-toluene sulfonic acid monohydrate and then followed by protection with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) to give compound **2**. According to the method described in the literature[31], **2** was oxidized with Dess–Martin oxidizing reagent to provide **3** (93.2%) and then followed by acylation of the hydroxyl group to yield **4** (85.1%). Wittig reaction of **4** with methyltriphenylphosphine bromide generated **5** (30.7%), which was then followed by sodium borohydride ($NaBH_4$) reduction to generate compound **6** (50.6%). The resulting alcohol **6** reacted with sodium periodate-saturated water in methanol at 0 °C to produce the ketone **7** in 93.7% yield. Protection of **7** with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) yielded compound **8** (46.6%). Peterson olefination of compound **8** with methyl(trimethylsilyl)acetate provided the methyl ester **9** (69.6%), which on reduction with diisobutylaluminum hydride (DIBAL-H) gave **10** (85.9%). The resulting alcohol **10** reacted with diphenylphosphine, and followed by oxidation with hydrogen peroxide to afford the desired A-ring phenylphosphine oxide **11**[37] (78.5%). Wittig–Horner coupling of **11** with the protected 25-hydroxy Grundmann's ketone **22** generated **12**[37] (37.6%), and followed by deprotection of TBDMS-protecting groups produced the target compound VS-105[37] (59.7%).

The synthesis of protected 25-hydroxy Grundmann's ketone **22** is described in Figure 4. Compound **13**, which was prepared from Vitamin D_2 according to the procedures described by Sardina et al.[29], was protected by triethylsilyl groups in the presence of 2,6-lutidine to give compound **14** (80%). Swern oxidation of **14** with oxalyl chloride and dimethyl sulfoxide (DMSO) afforded **15** in 80% yield. Oxidative cleavage of the aldehyde moiety in **15** with morpholine and cuprous chloride (CuCl) in the presence of oxygen

Table 2
The effects of VS-105 on serum calcium and PTH were determined in the 5/6 nephrectomized (NX) uremic rats in comparison to paricalcitol

	Ligand	First hypercalcemic dose (μg/kg)	First PTH suppressing dose (μg/kg)
5/6 NX uremic rats	VS-105	>0.6	0.004
	Paricalcitol	>0.08	0.02

Note: The methods for evaluating the in vivo potency of VDRMs in the 5/6 NX uremic rats have been published previously.[35,34,36]

to generate the methyl ketone **16** (38.7%). De-protection of **16** with tetra(*n*-butyl)ammonium fluoride gave **17**, and then followed by re-protection with acetyl group afforded ketone **18** (93.3%). Reductive etherification of **18** with trimethylsilyl ether **24** in the presence of trimethylsilyl-*O*-triflate and triethylsilane generated 22-Oxa C/D-ring methyl ester **19** (45.9%). Grignard reaction of **19** with methylmagnesium bromide yielded the diol **20** in high yield (98.3%). Dess–Martin periodinane oxidation of the diol **20** followed by protection with *tert*-butyldimethylsilyl group by reacting with trifluoromethanesulfonate (TBDMSOTf) produced the desired 22-Oxa C/D-ring ketone **22**[37] (44% from **20**). The trimethylsilyl ether **24** was made by protection of the commercial available methyl 3-hydroxy-(2*S*)-methyl-*n*-propanoate **23** with trimethylsilyl chloride in 65.1% yield.

Since many studies have been published on calcitriol and paricalcitol, biological evaluations were done for VS-105 using either calcitriol or paricalcitol as the 'bench-mark' compounds for comparison purposes. The in vitro data are summarized in Table 1. While the binding affinity of VS-105 to VDR is about fourfold less than that of calcitriol, VS-105 is more potent than calcitriol in inducing HL-60 differentiation and the expression of VDR reporter gene.

The effects of VS-105 and paricalcitol on serum calcium and PTH are compared in the 5/6 nephrectomized uremic rats and the results are summarized in Table 2. VS-105 is more potent than paricalcitol in suppressing serum PTH, but significantly less hypercalcemic than paricalcitol, suggesting a greatly widened therapeutic window (>50-fold vs 4-fold for paricalcitol).

In summary, by reviewing published papers on existing VDRMs and combining various changes at 20-epi, 22-oxa, 24-methyl, and 2-methylene, we identified VS-105 that binds to VDR with high affinity and is highly potent in inducing functional responses in vitro. More importantly, VS-105 effectively suppresses PTH in a dose range that does not affect serum calcium in the 5/6 NX uremic rats.

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37. *Satisfactory spectral characterization of all intermediates was obtained. Data for* ***11****:* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.68 (4H, m), 7.54–7.50 (2H, m), 7.48–7.44 (4H, m), 5.35 (1H, dd, *J* = 14.2, 6.8 Hz), 4.92 (2H, d, *J* = 12.7 Hz), 4.34 (2H, dd, *J* = 10.8, 4.9 Hz), 3.24–3.03 (2H, m), 2.33 (1H, dt, *J* = 12.7, 2.9 Hz), 2.08 (1H, ddd, *J* = 12.7, 7.8, 4.4 Hz), 2.02 (2H, d, *J* = 4.4 Hz), 0.86 (18H, s), 0.016 (6H, s), 0.007 (3H, s), −0.004 (3H, s). **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.23 (1H, d, *J* = 11.2 Hz), 5.81 (1H, d, *J* = 11.2 Hz), 4.97 (1H, s), 4.92 (1H, s), 4.42 (2H, dd, *J* = 8.8, 3.9 Hz), 3.51 (1H, dd, *J* = 8.8, 3.0 Hz), 3.25–3.19 (2H, m), 2.83 (1H, d, *J* = 13.2 Hz), 2.51 (1H, dd, *J* = 13.2, 5.9 Hz), 2.46 (1H, dd, *J* = 12.7, 4.4 Hz), 2.33 (1H, dd, *J* = 12.7, 2.5 Hz), 2.22–2.13 (2H, m), 2.01 (1H, t, *J* = 9.8 Hz), 1.78–1.10 (10H, m), 1.20 (3H, s), 1.12 (3H, s), 1.06 (3H, d, *J* = 5.8 Hz), 0.95 (3H, d, *J* = 6.8 Hz), 0.90 (9H, s), 0.86 (9H, s), 0.85 (9H, s), 0.55 (3H, s), 0.080 (3H, s), 0.069 (6H, s), 0.065 (3H, s), 0.049 (3H, s), 0.025 (3H, s). **22**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49 (1H, dd, *J* = 8.8, 3.0 Hz), 3.26 (1H, t, *J* = 8.8 Hz), 3.25–2.18(1H, m), 2.46 (1H, dd, *J* = 11.2, 7.3 Hz), 2.31–2.18 (3H, m), 1.93–1.82 (1H, m), 2.02–1.94 (1H, m), 1.80–1.69 (3H, m), 1.68–1.62 (1H, m), 1.57–1.52 (3H, m), 1.20 (3H, s),1.12 (3H, s), 1.07 (3H, d, *J* = 5.9 Hz), 0.95 (3H, d, *J* = 6.8 Hz), 0.85 (9H, s), 0.64 (3H, s), 0.069 (6H, s). **VS-105:** MS: *m*/*z* (%) 455 (19) $[M+Na]^+$, 315 (34), 297 (100), 279 (49), 149 (56), 74 (91), 59 (43). HRMS *m*/*z*: 455.3059 (Calcd for $C_{27}H_{44}O_4Na$: 455.3137). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (1H, d, *J* = 11.2 Hz), 5.86 (1H, d, *J* = 11.2 Hz), 5.10 (2H, d, *J* = 6.4 Hz), 4.52–4.42 (2H, m), 3.77 (1H, dd, *J* = 9.8, 4.4 Hz), 3.70 (1H, br s), 3.32 (1H, dd, *J* = 9.3, 5.4 Hz), 3.27 (1H, dd, *J* = 9.8, 5.9 Hz), 2.84 (1H, dd, *J* = 13.7, 4.9 Hz), 2.81 (1H, dd, *J* = 10.8, 3.9 Hz), 2.57 (1H, dd, *J* = 13.2, 3.9 Hz), 2.35–2.27 (2H, m), 2.14 (1H, d, *J* = 12.2 Hz), 2.03 (1H, t, *J* = 8.3 Hz), 1.81–1.41 (10H, m), 1.24 (3H, s), 1.16 (3H, s), 1.13 (3H, d, *J* = 5.9 Hz), 1.00 (3H, d, *J* = 7.3 Hz), 0.57 (3H, s); ^{13}C NMR (400 MHz, $CDCl_3$) δ 12.84, 13.87,18.34, 22.52, 23.46, 25.37, 25.92, 29.02, 29.29, 38.21, 40.14, 42.67, 45.64, 45.89, 55.84, 56.84, 70.75, 71.42, 71.87, 72.97, 78.87, 107.81, 115.39, 124.27, 130.63, 143.25, 152.09.