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Total synthesis of valerianananoids A, B, and C via autocatalytic diastereoselective domino Michael reaction

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Abstract—Natural enantiomers of unique tricyclic sesquiterpenoids, valerianananoids A–C **1**–**3**, have been synthesized starting from bicyclo[2.2.2]octane-2,5-dione derivative **11**, which was obtained by diastereoselective catalytic domino Michael reaction of oxophorone **5** with 8-phenylmenthyl acrylate **10** by LDA or silica-gel-base (NMAP-Li). The tricyclic ring was closed selectively by intramolecular 6-*endo-trig* mode cyclization of the ketyl radical, which was generated from keto-allylether **25** by either lithium or sodium naphthalenide.

1. Introduction

A folk medicine prepared from rhizomes and roots of *Valeriana fauriei* has been used for sedative and antispasmodic purposes in Japan. Similarly in China, roots of *Valeriana jatamansii* have been utilized as a folk medicine, which has hypnotic, tranquilizing, and antiviral activities. In 1995, Takeya and co-workers investigated the ethyl acetate extracts of the roots of *V. fauriei* and identified two new tricyclic sesquiterpenoids, 8-hydroxy- and 8-acetoxypatchouli alcohols **2** and **3**,[1] which have a unique carbon framework as that of seychellene[2] or patchouli alcohol **4**.[3] Subsequently in 1997, Yu and co-workers reported the isolation and the structure determination of three sesquiterpenoids from *V. jatamansii* (Fig. 1), and named independently these compounds valerianananoids A **1**, B **2**, and C **3**.[4] Collado et al. reported the formation of the diol **2** as a minor metabolite in the biotransformation of patchouli alcohol **4** by the fungus *Botrytis cinerea*.[5] The relative stereochemistry of valerianananoid A **1** was elucidated by a single crystal X-ray analysis, whereas configurations of the hydroxy groups of B **2** and C **3** were assigned by NOE experiment.[4] Absolute configuration of **1** was suggested employing CD octant rule,[4] though application of empirical rule to the compound having very small extinction coefficient of the spectrum created some ambiguity on the absolute stereochemistry.

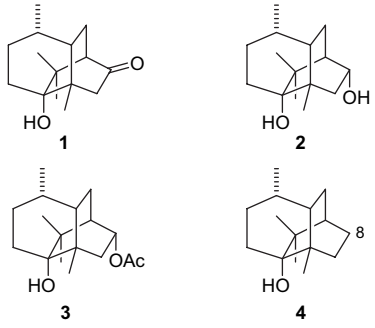

Figure 1. Valerianananoids A–C **1**–**3** and pachouli alcohol **4**.

Our ongoing interest toward the total synthesis of bi- and tricyclic natural products via the domino Michael protocol[6] prompted us to investigate the synthesis of these natural products and led us to report already the first total synthesis of racemic valerianananoid A **1** via Lewis acid catalyzed domino Michael strategy starting from oxophorone **5** followed by intramolecular 6-*endo-trig* cyclization of a ketyl radical.[7] Recently, Srikrishna and Satyanarayana have also reported the total synthesis of these compounds **1**–**3** in natural enantiomeric form via similar domino Michael strategy[8] starting from (*R*)-carvone,[9] in which relative and absolute stereochemistries of **1**–**3** have been established.

2. Results and discussion

We disclose herein diastereoselective total synthesis of valerianananoid A **1** and its congeners **2** and **3** in enantiomerically pure form via an autocatalytic diastereoselective domino Michael reaction.

The synthetic strategy is outlined in Scheme 1. A tricyclic compound **9**, an immediate precursor of valerianananoid A **1**,

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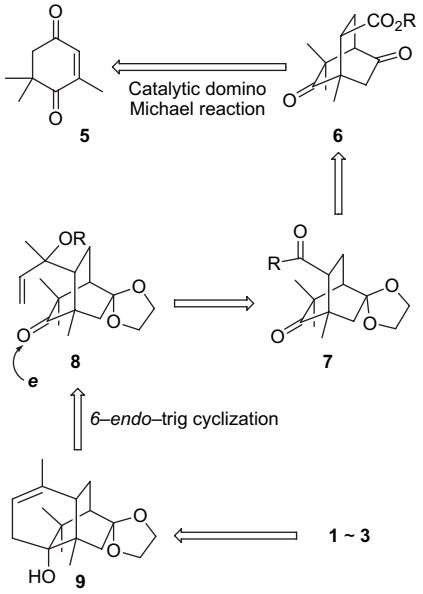
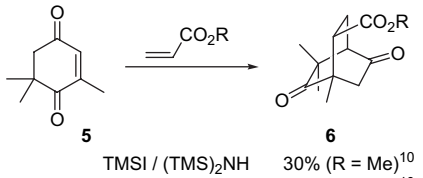
could be obtained by intramolecular 6-*endo-trig* mode cyclization of a ketyl radical generated on a bicyclic allylether **8**, which in turn could be synthesized from the domino Michael product **6** of oxophorone **5** followed by equilibration of the carbonyl unit to the same side as the carbonyl group leading to **7**.



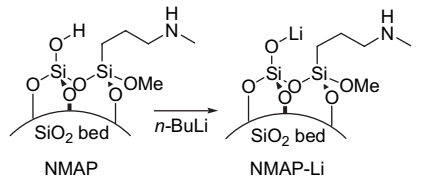
Scheme 1. Synthetic strategy.

In our previous domino Michael reaction leading to the bicyclic compound **6**, silyl enol ether of oxophorone **5** and methyl acrylate were employed in the presence of diethylaluminum chloride,[10] because the domino reaction of oxophorone **5** under basic reaction condition provided capricious results (Scheme 2). However, we recently found that a catalytic amount of LDA is sufficient to provide the bicyclic compound **6**, and indicated that the reaction was catalyzed by the enolate of the product as a base (autocatalytic pathway).[11] Subsequently, it was found that a Brönsted base (NMAP-Li) generated on *N*-methylaminopropylated silica-gel (NMAP) surface also catalyzed the reaction (Equation 1, Scheme 2).[12] It is worthy of note that the NMAP pellets could be re-used up to six times.



TMSI / $(TMS)_2NH$	30% (R = Me)[10]
LDA (1 eq)	21% (R = Me)[10]
LDA (0.1 eq)	92% (R = Cy)[11]
NMAP-Li (0.1 eq)/ HMPA	90% (R = Cy)[12]

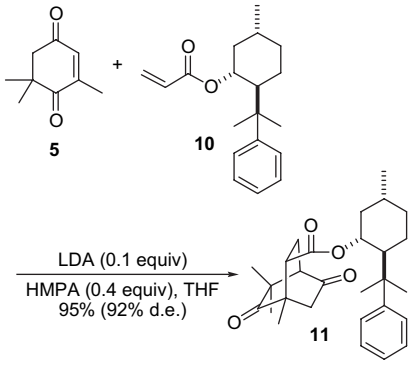
Scheme 2. Domino Michael reaction of oxophorone.



Equation 1. Reversed phase silica-gel and its conjugated base.

One issue of the present synthetic strategy is how to prepare the optically pure bicyclic compound **6**. Enantioselective domino Michael reaction leading to optically active bicyclo[2.2.2]octane-2,5-dione framework has not been reported in spite of extensive efforts. In diastereoselective domino Michael reaction, there have been several precedents, in which the reaction with acrylate having chiral auxiliary in α,β-unsaturated carboxylate moiety exhibited successful diastereoselectivity.[13] On the other hand, the result of the reaction with acrylate having chiral auxiliary in an alkoxy portion was not fruitful. Actually, the domino Michael reaction of isophorone with 8-phenylmenthyl acrylate **10** recorded only about 40% diastereoselection.[14]

Based on these backgrounds, it was challenging to investigate a diastereoselective catalytic domino Michael reaction of oxophorone **5** with 8-phenylmenthyl acrylate **10** (Scheme 3). Fortunately, the domino Michael reaction with oxophorone **5** and 8-phenylmenthyl acrylate **10** proceeded in the presence of 0.1 equiv of LDA to furnish separable bicyclic compound **11** and its diastereomer in highly diastereoselective manner (92% de) in high yield (96%) (Scheme 3). The reaction was catalyzed also by NMAP-Li[12] with the same efficiency as LDA. Recrystallization from *n*-hexane provided single crystals. Relative as well as absolute stereochemistry of the domino Michael product **11** was established by an X-ray crystallography, since the absolute stereochemistry of phenylmenthyl moiety was known (Fig. 2).



Scheme 3. Diastereoselective catalytic domino Michael reaction.

The stereochemical outcome of the diastereoselective reaction is easily understood by the approach of the enolate of oxophorone **5** to *si*-face of the acrylate **10**, which reacted with *s-cis* conformation (Fig. 3). The phenyl group on the menthyl moiety works very effectively as a steric shielding in this particular reaction, which is recognized from the ORTEP drawing of **11** (Fig. 3) providing that the conformation is the same in solution, Moreover, increased steric bias of the α-axial methyl group of the dienolate of oxophorone **5** than that of isophorone might facilitate approach of the acrylate **10** to the β-face of the dienolate of **5**. Very high diastereocontrol is worthy of note.

With optically active bicyclic compound **11** in hand, a synthetic study of valerianananoids **1**–**3** started (Scheme 4). Conventional ketalization of the bicyclic compound **11** allowed

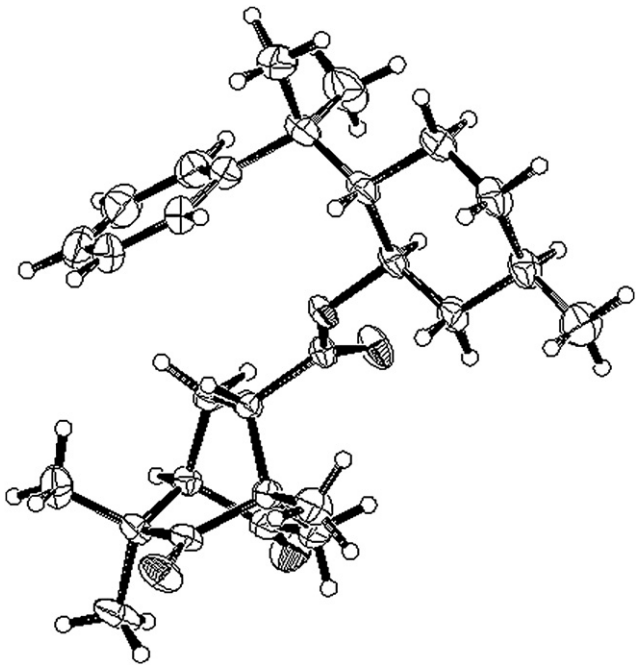


Figure 2. An ORTEP drawing of **11**.

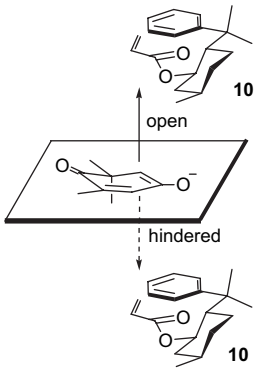
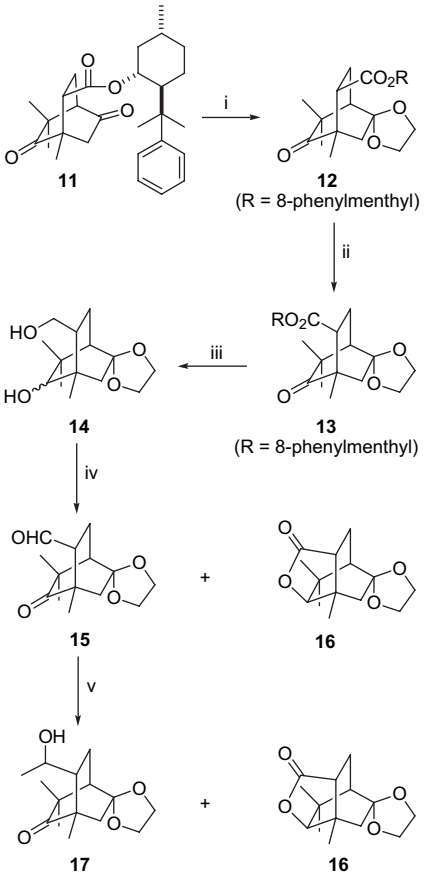


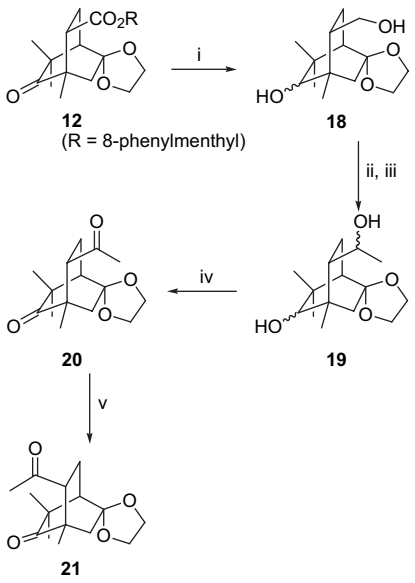
Figure 3. Diastereoselective domino Michael reaction.



Scheme 4. Reagents, conditions, and yields: (i) ethylene glycol, PTSA, benzene, reflux, 100%; (ii) KOH, EtOH, reflux, 76% for **13**, 23% for **12**; (iii) $LiAlH_4$ (1.5 equiv), THF, reflux, 90%; (iv) PCC, AcONa, MS-4 Å, CH_2Cl_2, rt, 69–95% (inseparable mixture of **15** and **16**); (v) MeLi (1.5 equiv), THF, −78 to −10 °C.

selective protection of the less congested ketone to provide ketal **12** quantitatively. Base catalyzed isomerization of **12** under reflux of ethanolic solution of potassium hydroxide resulted in an equilibrium mixture of **12** and **13** in 23 and 76% yields, respectively. Steric bulkiness of 8-phenylmenthyl moiety might circumvent complete isomerization into **13**, since methyl ester equivalent of **12** resulted in complete isomerization in the previous racemic total synthesis.[7] Lithium aluminum hydride (LAH) reduction of the keto-ester **13** in refluxing THF provided the diol **14** and 8-phenylmenthol in 90 and 93% yields, respectively. Repeated PCC oxidation of the diol **14** afforded an inseparable mixture of the desired keto-aldehyde **15** and the lactone **16** in varying yields. Other methods of oxidation including Swern and its modified procedure were unsuccessful. Attempted formation of methylketone from the lactone **16** by addition of methyllithium to the mixture of **15** and **16** resulted in unsatisfactory results.

In order to solve several issues cited above, an alternative synthetic sequence was designed, in which several advantages were expected as follows. (1) Removal of the chiral auxiliary at earlier stage of the synthetic sequence would improve efficiency of recovery of 8-phenylmenthol. (2) Formation of the lactone **16** (Scheme 4) would be prevented by oxidation of *anti*-diol **18**. (3) Equilibration from **20** to **21** would be much easier (Scheme 5) than equilibration from **12** to **13** due to the absence of bulky phenylmenthyl group. (4) Difficulty to separate **12** and **13** due to similar polarity would be solved (Scheme 4). To this end, the ketal **12** was reduced with LAH in refluxing THF to give a separable diastereomeric mixture of diol **18** (less polar/more polar diastereomer=3:1) and 8-phenylmenthol in 96 and 100% yields, respectively (Scheme 5). The major less polar diastereomer has an *endo*-secondary hydroxyl group judged from W-type coupling as shown in Figure 4. Swern oxidation of the mixture of the diol **18** provided the keto-aldehyde, which was reacted with methylmagnesium bromide to give alcohol **19** selectively in 90% yield in two steps. Addition of methyllithium was not effective even in the presence of HMPA or $CeCl_3$. Subsequent PCC oxidation afforded methylketone **20** in 98% yield. Treatment of the methylketone **20** with potassium hydroxide in methanol resulted in an equilibrium mixture of the desired *endo*-methylketone **21** and recovered starting ketone **20** in 81 and 12% yields, respectively, which were separated easily by recrystallization. Equilibrium ratio was apparently improved employing the methylketone **20** rather than the ester **12**. The relative stereochemistry of **21** was confirmed by the disappearance of the W-type long range



Scheme 5. Reagents, conditions, and yields: (i) $LiAlH_4$ (4 equiv), THF, reflux, 96% (less polar/more polar isomer=3:1); (ii) oxalyl chloride (3 equiv), DMSO, Et_3N, CH_2Cl_2, −78 °C; (iii) MeMgBr (3 equiv), THF, 90% in two steps; (iv) PCC (2 equiv), AcONa, MS-4 Å, CH_2Cl_2, rt, 98%; (v) KOH, MeOH, reflux, 81%.

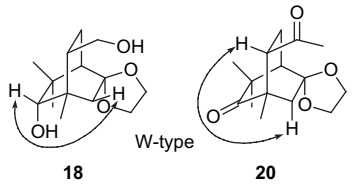
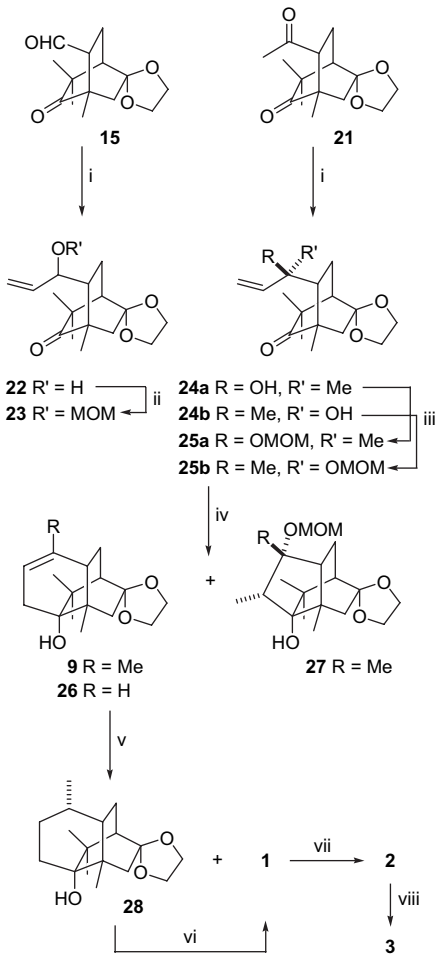


Figure 4. Relative stereochemistries of the less polar diol **18** and the methylketone **20**.

coupling between an *endo*-proton next to the ketal group and a proton on a carbon bearing an acyl group (Fig. 4).

With the requisite methylketone **21** in hand, closure of the third ring was investigated by 6-*endo-trig* mode radical cyclization (Scheme 6).[16] Addition of vinylmagnesium chloride in THF at −30 °C to −20 °C to the methylketone **21** furnished two separable less polar (22%) and more polar diastereomers (58%). In diethyl ether, no diastereoselectivity was observed. Addition of cerium chloride, magnesium bromide or HMPA did not change diastereomeric ratio or total yield. The relative stereochemistries of **24a** and **24b** were determined from the relative stereochemistry of MOM-ether **27** (vide infra) by NOE experiments (Fig. 5). This result indicates that vinylmagnesium chloride attacked the less hindered *re* face of the carbonyl group of **21** from its outer face. Addition at low temperature was critical to realize good yield. The more polar diastereomer **24a** was protected with excess methoxymethylchloride (MOMCl) and diisopropylethylamine to provide methoxymethyl (MOM) ether **25a** at 60 °C in 89% yield. The less polar diastereomer **24b** was also transformed into MOM-ether **25b** at 60 °C in 95% yield.

In order to close the third ring, we initially employed a method by Bertrand[16] and Spreitzer[17] employing sodium in refluxing THF. The reaction of MOM-ether **23** under the reaction condition was successful to give the tricyclic compound **26** in 61% yield. However, cyclization of the MOM-



Scheme 6. Reagents, conditions, and yields: (i) vinylmagnesium chloride (5 equiv), THF, −20 °C, 80%; (ii) MOMBr (4 equiv), NaH, THF, 0 °C, 75%; (iii) MOMCl (5 equiv), $(i\text{-Pr})_2NEt$ (6 equiv), DMF, 89% for **25a** and 95% for **25b**; (iv) see Table 1; (v) H_2, Pd–C, AcOEt, rt; (vi) PTSA, H_2O, THF, rt, 90% in two steps; (vii) $NaBH_4$ (20 equiv), MeOH, rt, 99%; (viii) Ac_2O (10 equiv), Py, DMAP, CH_2Cl_2, 0 °C, 99%.

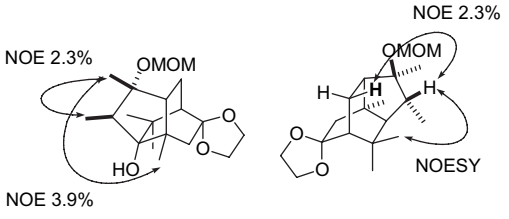


Figure 5. Relative stereochemistry of **27**.

ether **25a** in a similar manner in the presence of HMPA provided the desired product **9** in 44% yield (Table 1, entry 2). In order to improve both yield and 6-*endo*- versus 5-*exo-trig* selectivity,[15] more active reducing reagent which is applicable at low temperature was investigated, and the cyclization was improved remarkably employing lithium or sodium naphthalenide in THF at −55 °C to give **9** in 94 or 95% yield, respectively. The reaction by samarium iodide in the presence or absence of HMPA (entry 1), or zinc with titanium tetrachloride resulted in low yields (entry 3). On the other hand, the reaction of diastereomeric MOM-ether **25b** with lithium naphthalenide in THF resulted in formation of 5-*exo-trig* product **27** as a major product (entry 6). Fortunately,

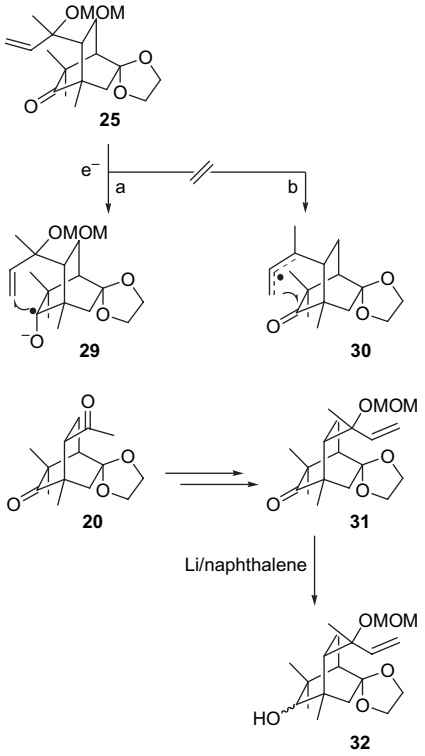
Table 1. Ketyl radical cyclization of MOM-ethers **25a** and **25b**

Entry	Substrate	Solvent	Reducing agent	Reaction condition	Yield (%)		
					9	**27**	**25**
1	**25a**	THF/HMPA	SmI_2/Sm/*t*-BuOH	0 °C–reflux	20	6	50
2			Na	Reflux	44		
3		THF	$Zn/TiCl_4$	−20–rt	—	—	89
4			Li/naphthalene	−55 °C	94	—	—
5			Na/naphthalene	−55 °C	95	—	—
6	**25b**		Li/naphthalene	−55 °C	33	46	
7		THF/HMPA			Trace	14	84
8		Diethyl ether			15	35	29
9		THF/Et_3N			32	25	12
10		THF/dioxane			54	29	

this unfavorable selectivity was improved to reverse the ratio of 5-*exo*- versus 6-*endo-trig* product ratio employing THF and dioxane (3:2) and to provide **9** (54%) and **27** (29%), respectively (entry 10). Since dioxane has lower electron donor number and thus has the lowest Lewis basicity than other solvents tested, destabilization of lithium cation might be effective in the desired selectivity.[18]

The relative stereochemistry of the MOM-ether **27** was established by NOE experiments as shown in Figure 5. Since the MOM-ether **27** was obtained from **25b**, the relative stereochemistries of **24a**, **24b**, **25a**, and **25b** were established as shown in Scheme 6.

In the present cyclization, there might be two alternative pathways. One is the initial generation of the allyl radical[19] followed by intramolecular addition to carbonyl group (Scheme 7, path b) and the other is initial generation of ketyl radical followed by intramolecular addition to vinyl group of the allyloxy moiety (Scheme 7, path a). In order to justify the pathway, compound **31** was synthesized and subjected to radical cyclization with lithium naphthalenide at −55 °C, which resulted only in reduction of the carbonyl group. The allyloxy moiety of **31** was intact under the reaction condition. Thus, it is clear that the present cyclization started from ketyl radical formation.

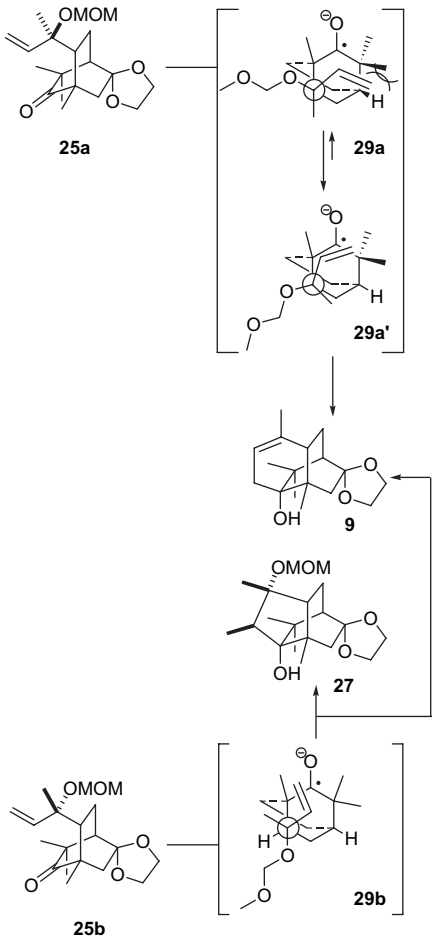


Scheme 7. Formation of ketyl radical.

In order to evaluate selectivity between 6-*endo*- and 5-*exo-trig* ketyl radical cyclizations, two assumptions were made. (1) The reaction proceeds under kinetic control. (2) The vinyl group in the substrate **25a** or **25b** orients *anti* to MOM-oxy group due to 1,3-allylic strain. Based on these assumptions, stable conformer of the ketyl radical from **25a** was postulated to be **29a′** due to the less steric congestion mainly with a methyl group according to molecular model inspection (Scheme 8). Thus, subsequent intramolecular cyclization provided 6-*endo-trig* product **9** specifically in high yield. On the other hand, the conformer **29b** derived from **25b** is the stable conformer to give both 6-*endo*- and 5-*exo-trig* products **9** and **27**.

Final transformation was conventional. Catalytic hydrogenation of the olefin **9** proceeded selectively from the less hindered outer *si*-face of **9** to give ketal **28**, which was deprotected in 90% yield in two steps to furnish valerianannoid A **1** (Scheme 6). Reduction of **1** with sodium borohydride provided in 99% yield valerianannoid B **2**, which was acetylated to give valerianannoid C **3** in 99% yield. The spectral data of these compounds were identical with those kindly provided by Professors Yu and Srikrishna. The optical rotations of valerianannoids B and C were identical with those reported by Itokawa et al.[1] However, a large difference was observed between our synthetic $\{[\alpha]_D^{20}$ −82.3 (*c* 0.266, $CHCl_3)\}$ and natural valerianannoid A[4] $\{[\alpha]_D^{20}$ −34.6 (*c* 0.231, $CHCl_3)\}$. Synthetic valerianannoid A by Srikrishna[9] also had different optical rotational value $\{[\alpha]_D^{24}$ −33.3 (*c* 0.3, $CHCl_3)\}$. To this end, valerianannoid B **2** was synthesized from the domino Michael product **11** of 92% de and transformed into its (*S*)-MTPA-ester with DCC. The NMR spectrum of the MTPA-ester exhibited the diastereomeric excess of 91%. Since there was no procedure that destroys enantioselectivity during the synthetic sequence, the present absolute value of optical rotation must be proper.

In summary, we have completed the total synthesis of valerianannoid A **1** in 12 steps in 34% overall yield from oxophorone **5** along with valerianannoid B **2** and C **3** via autocatalytic



Scheme 8. Selectivity between 6-*endo*- and 5-*exo-trig* cyclizations.

diastereoselective domino Michael reaction to construct the bicyclic framework and subsequent ketyl radical cyclization to close the tricyclic ring. Value of optical rotation of valerianananoid A **1** was corrected.

3. Experimental

3.1. General

THF was distilled from benzophenone ketyl prior to use. Dichloromethane was distilled from CaH_2 prior to use. NMR spectra were measured in $CDCl_3$ with TMS as internal standard on Varian Unity 500 plus (500 MHz), JNM-EXCALIBUR (270 MHz), or Varian Gemini-200 at room temperature. IR spectra were recorded on Shimadzu FTIR-4200 using sodium chloride optics. Mass spectra were recorded on JMS-GCMATE BU-20 using EI method. Analytical TLC was carried out on Kieselgel 60 F_{254} plates employing *n*-hexane/ethyl acetate as the mobile phase. Product was purified by medium pressure liquid chromatography (MPLC) with *n*-hexane/ethyl acetate as an eluent.

3.1.1. (2*S*,1*R*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl (1*S*,2*S*)-1,5,5-trimethyl-6,8-dioxobicyclo[2.2.2]-octane-2-carboxylate (11). To a stirred solution of diisopropylamine (90 μL, 0.69 mmol) in THF (20 mL) was added *n*-butyllithium (440 μL, 1.59 M solution in *n*-hexane, 0.69 mmol) at 0 °C under nitrogen atmosphere. To the solution was added oxophorone **5** (1.263 g, 8.30 mmol) in THF (15 mL) at −78 °C. After being stirred for 15 min, a solution of (−)-8-phenylmenthyl acrylate **10** (1.977 g, 6.90 mmol) in THF (15 mL) and subsequently HMPA (480 μL, 2.76 mmol) were added dropwise. The solution was stirred for 14 h to −40 °C. The reaction was quenched by 1 N hydrochloric acid. The product was extracted with ethyl acetate twice. The organic layer was washed with water, brine and dried over anhyd sodium sulfate. Evaporation of the solvent and Kugel-Rohr distillation (80–100 °C, 2 mmHg) left crude product, which was recrystallized from hexane three times to afford enantiomerically pure domino Michael product **11** (2.685 g, 89%, colorless crystals). The mother liquor was purified by medium pressure LC (eluent: ethyl acetate/*n*-hexane=1:3) to give **11** (117 mg, 3%) and its diastereomer (120 mg, 4%): mp 105–106 °C; $[\alpha]_D^{20}$ +50.2 (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 3051, 2403, 1723, 1240, 1224, 1196, 908 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.84 (s, 3H), 0.89 (d, *J*=6.5 Hz, 3H), 0.99 (s, 3H), 1.13 (s, 3H), 1.16 (s, 3H), 1.25 (s, 3H), 0.80–1.30 (m, 2H), 1.35–1.62 (m, 3H), 1.62–1.80 (m, 1H), 1.94 (dd, *J*=1.6, 19.6 Hz, 1H), 1.80–2.22 (m, 5H), 2.33 (t, *J*=2.8 Hz, 1H), 2.81 (d, *J*=19.6 Hz, 1H), 4.76 (dt, *J*=10.8, 4.3 Hz, 1H), 7.00–7.13 (m, 1H), 7.18–7.35 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.2 (q), 21.8 (q), 22.2 (q), 23.0 (q), 23.3 (t), 24.9 (t), 26.0 (q), 30.3 (q), 31.2 (d), 34.4 (t), 39.3 (s), 41.0 (d), 41.1 (t), 41.5 (t), 43.8 (s), 47.8 (s), 49.9 (d), 55.7 (d), 75.4 (d), 124.7 (d), 125.0 (d), 127.7 (d), 152.3 (s), 172.0 (s), 209.8 (s), 214.8 (s); HRMS *m/z* calcd for $C_{28}H_{38}O_4$ 438.2770, found 438.2769.

3.1.2. (2*S*,1*R*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl (6*S*,7*S*)-6,10,10-trimethyl-11-oxospiro[1,3-dioxolane-2,8′-bicyclo[2.2.2]octane]-7-carboxylate (12). A stirred mixture of the diketone **11** (308 mg, 0.71 mmol), ethylene glycol (0.40 mL, 7.2 mmol), and *p*-toluenesulfonic acid (18 mg, 0.093 mmol) in benzene was heated at reflux for 17 h in a Dean–Stark water separator under nitrogen atmosphere. After addition of aq sodium hydrogen carbonate, the product was extracted with ethyl acetate twice. The organic layer was washed with water, brine and dried over anhyd sodium sulfate and evaporated to dryness. The residue was purified by medium pressure LC (eluent: ethyl acetate/*n*-hexane=2:5) to give the ketal **12** (338 mg, 100%, colorless amorphous solid): $[\alpha]_D^{20}$ +42.7 (*c* 1.01, $CHCl_3$); IR ($CHCl_3$) 3115, 2961, 1717, 1460, 1385, 1190, 1093 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.76 (s, 3H), 0.87 (d, *J*=6.8 Hz, 3H), 1.07 (s, 3H), 1.16 (s, 3H), 1.26 (s, 6H), 1.60 (dd, *J*=1.6, 15.2 Hz, 1H), 1.80–1.89 (m, 2H), 2.02–2.15 (m, 1H), 2.30–2.41 (m, 1H), 2.45 (d, *J*=15.2 Hz, 1H), 0.91–1.95 (m, 8H), 3.80–3.98 (m, 4H), 4.78 (dt, *J*=10.8, 4.3 Hz, 1H), 7.00–7.10 (m, 1H), 7.18–7.32 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.8 (q), 21.8 (q), 23.0 (q), 23.5 (t), 25.4 (q), 26.3 (t), 26.6 (q), 29.6 (q), 31.3 (d), 34.5 (t), 39.4 (s), 40.4 (t), 40.6 (d), 41.7 (t), 43.8 (s), 45.6 (d), 46.5 (s), 50.0 (d), 63.3 (t), 64.0 (t), 75.0 (d), 109.2 (s), 124.7 (d), 125.0 (d), 127.7 (d), 152.2 (s), 172.5 (s), 217.7 (s); HRMS *m/z* calcd for $C_{30}H_{42}O_5$ 482.3032, found 482.3036.

3.1.3. (2*S*,1*R*,5*R*)-5-Methyl-2-(1-methyl-1-phenylethyl)-cyclohexyl (6*S*,7*R*)-6,10,10-trimethyl-11-oxospiro[1,3-dioxolane-2,8′-bicyclo[2.2.2]octane]-7-carboxylate (13). A solution of the acetal **12** (500 mg, 1.04 mmol) and potassium

hydroxide (90 mg, 1.60 mmol) in ethanol (35 mL) was heated at reflux for 23 h. The reaction was quenched by addition of 1 N hydrochloric acid. The product was extracted with ethyl acetate twice. The organic layer was washed with water, brine and dried over anhyd sodium sulfate. Evaporation of the solvent followed by medium pressure LC (eluent: ethyl acetate/*n*-hexane=1:4) of the residue provided the *endo*-product **13** (378 mg, 76%) along with recovered starting material **12** (117 mg, 23%, colorless amorphous solid).

endo-Product **13**: mp 119 °C; $[\alpha]_D^{20}$ −36.0 (*c* 1.02, $CHCl_3$); IR ($CHCl_3$) 3046, 2402, 1728, 1194, 1096, 814 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.70–2.06 (m, 9H), 0.85 (d, *J*=6.4 Hz, 3H), 0.98 (s, 3H), 1.18 (s, 3H), 1.21 (s, 3H), 1.26 (s, 3H), 1.32 (s, 3H), 1.60 (ddd, *J*=13.3, 6.7, 2.4 Hz, 1H), 1.80 (d, *J*=14.9 Hz, 1H), 1.91 (d, *J*=14.9 Hz, 1H), 2.26 (ddd, *J*=13.3, 11.6, 3.4 Hz, 1H), 2.44 (dd, *J*=11.6, 6.7 Hz, 1H), 3.80–4.05 (m, 4H), 4.78 (td, *J*=10.6, 4.3 Hz, 1H), 7.00–7.50 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.0, 22.4, 24.5, 25.6, 26.1, 27.6, 28.5, 31.9, 35.1, 40.7, 42.1, 45.4, 46.4, 46.8, 50.8, 63.7, 64.9, 75.9, 109.9, 125.8, 126.1, 128.6, 151.7, 174.2, 217.8; HRMS *m/z* calcd for $C_{30}H_{42}O_5$ 482.3032, found 482.3036.

3.1.4. (6*S*,11*R*)-11-(Hydroxymethyl)-6,8,8-trimethylspiro[1,3-dioxolane-2,8′-bicyclo[2.2.2]octane]-7-ol (14). To a stirred slurry of LAH (24 mg, 0.64 mmol) in THF (10 mL) was added the menthyl ester **13** (125 mg, 0.26 mmol) in THF under nitrogen atmosphere. After being heated at reflux for 3 h, the reaction was quenched by addition of aq ammonium chloride. After decantation of the organic layer, the residue was rinsed with ethyl acetate. The combined organic layer was dried over anhyd sodium sulfate and evaporated to dryness. The residue was purified by column chromatography (eluent: ethyl acetate/*n*-hexane=1:5 to 3:1) to give the diol **14** (60 mg, 90%, colorless crystals) and 8-phenylmenthol (56 mg, 93%): mp 114 °C; $[\alpha]_D^{20}$ −66.2 (*c* 0.99, $CHCl_3$); IR ($CHCl_3$) 3632, 3392, 3051, 2922, 1479, 1456, 1134, 1099, 1064, 1005, 956 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.06 (s, 3H), 1.17 (s, 3H), 1.40 (d like, *J*=3.2 Hz, 1H), 1.54 (dd, *J*=14.3, 1.0 Hz, 1H), 1.75 (d, *J*=14.3 Hz, 1H), 1.83–2.00 (m, 2H), 3.12 (s, 1H), 3.47 (dd, *J*=11.4, 3.2 Hz, 1H), 3.46–3.73 (br s, 2H), 3.81 (dd, *J*=11.4, 1.6 Hz, 1H), 3.80–4.00 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.8 (t), 22.3 (q), 25.1 (q), 33.3 (q), 26.5 (s), 40.0 (d), 45.4 (d), 49.8 (t), 60.9 (t), 63.5 (t), 64.3 (t), 82.0 (d), 111.6 (s). Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.59; H, 9.44. Found: C, 65.46; H, 9.47.

3.1.5. (6*S*,7*R*)-6,10,10-Trimethyl-11-oxospiro[1,3-dioxolane-2,8′-bicyclo[2.2.2]octane]-7-carbaldehyde (15) and (12*S*)-12,15,15-trimethyl-10-oxaspiro[1,3-dioxolane-2,9′-tricyclo[4.3.1.0^{3,7}]decane]-9-one (16). A mixture of PCC (268 mg, 1.24 mmol), sodium acetate (103 mg, 1.26 mmol), MS-4 Å (one pellet), and Celite (503 mg) was evacuated for 1 h at rt. To the mixture was added dichloromethane (2 mL) and then a solution of the diol **14** (32 mg, 0.12 mmol) in dichloromethane (3 mL) under nitrogen atmosphere. After being stirred for 30 min, the organic layer was passed through silica-gel short column. The residue was rinsed with ethyl acetate. Evaporation of the solvents followed by column chromatography and subsequent medium pressure LC (eluent: ethyl acetate/*n*-hexane=2:1) afforded an inseparable mixture of the aldehyde **15** and the lactone **16** in 3:1 ratio (NMR).

Aldehyde **15**: IR (CCl_4) 3410, 2973, 2934, 2880, 1788, 1722, 1458, 1358, 1230, 1093, 1035 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (s, 3H), 1.18 (s, 3H), 1.28 (s, 3H), 1.84 (dd, *J*=3.1, 2.9 Hz, 1H), 2.02 (m, 2H), 2.04 (ddd, *J*=14.3, 6.9, 2.3 Hz, 1H), 2.23 (ddd, *J*=14.3, 10.8, 3.6 Hz, 1H), 2.77 (ddd, *J*=10.8, 6.9, 3.6 Hz, 1H), 3.87–4.05 (m, 4H), 9.52 (d, *J*=3.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.8 (q), 19.8 (t), 24.4 (q), 26.6 (q), 45.2 (d), 45.7 (s), 46.0 (s), 46.6 (d), 52.0 (t), 63.2 (t), 64.9 (t), 109.0 (s), 201.7 (s), 218.0 (s).

Lactone **16**: mp 71–72 °C; IR (CCl_4) 2994, 1776, 1469, 1362, 1128, 1086, 1019, 978 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.11 (s, 3H), 1.14 (s, 3H), 1.81 (m, 1H), 1.89 (ddd, *J*=14.8, 3.6, 1.5 Hz, 1H), 1.95 (d, *J*=8.6 Hz, 2H), 2.05–2.18 (m, 1H), 2.41 (ddd, *J*=14.8, 10.8, 2.2 Hz, 1H), 3.73 (s, 1H), 3.80–4.01 (m, 4H); HRMS *m/z* calcd for $C_{14}H_{20}O_4$ 252.1361, found 252.1361.

3.1.6. (6*S*,11*R*)-11-(Hydroxyethyl)-6,8,8-trimethylspiro[1,3-dioxolane-2,8′-bicyclo[2.2.2]octane]-7-one (17). To a solution of the aldehyde **15** and the lactone **16** (29 mg, 0.12 mmol) in THF (2 mL) was added ethereal solution of methyllithium (172 μL, 0.98 M, 0.17 mmol) at −78 °C under nitrogen atmosphere. After being stirred for 7 h at −78 °C to −10 °C, the reaction was quenched by addition of aq ammonium chloride. The product was extracted with ethyl acetate twice. The combined organic layer was washed with water, brine and dried over anhyd sodium sulfate. Evaporation of the solvent followed by medium pressure LC (eluent: ethyl acetate/*n*-hexane=2:1) provided a mixture of the alcohol **17** and lactone **16** (26 mg): IR ($CHCl_3$) 3605, 2978, 2930, 2882, 1714, 1481, 1460, 1350, 1101, 1037, 1014, 468 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.11 (d, *J*=6.5 Hz, 3H), 1.22 (s, 3H), 1.24 (s, 3H), 2.10–1.70 (m, 6H), 4.05–3.80 (m, 4H), 4.18–3.05 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.2 (q), 19.0 (t), 20.7 (q), 24.5 (q), 26.9 (q), 44.6 (s), 45.5 (d), 46.3 (t), 46.7 (d), 47.0 (s), 62.8 (t), 63.8 (t), 64.6 (d), 109.5 (s), 222.0 (s). Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.01. Found: C, 67.18; H, 9.12.

3.1.7. (6*S*,11*S*)-11-(Hydroxymethyl)-6,8,8-trimethylspiro[1,3-dioxolane-2,8′-bicyclo[2.2.2]octane]-7-ol (18). A mixture of the ketal **12** (28 mg, 0.058 mmol) and LAH (8 mg, 0.20 mmol) in THF (4 mL) was heated at reflux for 2 h under nitrogen atmosphere. The reaction was quenched by addition of aq ammonium chloride. After decantation of the organic layer, the residue was rinsed with ethyl acetate. The combined organic layer was evaporated in vacuo. The residue was purified by column chromatography (eluent: ethyl acetate/*n*-hexane=1:3 to 3:1) to give 8-phenylmenthol (14 mg, 100%). Combined polar fractions were purified again by medium pressure LC (eluent: ethyl acetate/*n*-hexane=3:1) to provide the diol **18** (less polar diastereomer: 11 mg, 71%, more polar diastereomer: 4 mg, 25%).

More polar **18**: mp 166–167 °C; $[\alpha]_D^{20}$ +38.5 (*c* 0.954, $CHCl_3$); IR ($CHCl_3$) 3636, 3455, 2930, 1410, 1356, 1244, 1089, 1013, 953 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$)

δ 0.94 (s, 3H), 1.04 (s, 3H), 1.23 (s, 3H), 1.44 (dd, J=15.0, 1.4 Hz, 1H), 2.06 (d, J=15.0 Hz, 1H), 1.35–2.10 (m, 4H), 3.17 (s, 1H), 3.62–3.75 (m, 2H), 3.75–4.05 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.4 (q), 24.0 (q), 24.2 (t), 31.4 (q), 32.0 (d), 35.9 (s), 38.5 (s), 43.3 (t), 44.6 (d), 62.7 (t), 63.9 (t), 64.7 (t), 83.2 (d), 110.7 (s); HRMS m/z calcd for $C_{14}H_{24}O_4$ 256.1674, found 256.1676.

Less polar **18**: mp 91–92 °C; $[\alpha]_D^{20}$ +51.6 (c 0.988, $CHCl_3$); IR ($CHCl_3$) 3624, 3488, 3003, 1468, 1348, 1229, 1194, 1096, 1014, 953 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.11 (s, 3H), 1.17 (s, 3H), 1.39 (dd, J=3.8, 2.1 Hz, 1H), 1.58 (dd, J=13.8, 2.1 Hz, 1H), 1.64–1.77 (m, 2H), 1.92 (ddd, J=13.8, 10.3, 3.8 Hz, 1H), 2.99 (d, J=6.2 Hz, 1H), 3.60–3.81 (m, 2H), 3.81–4.05 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.5 (q), 24.3 (t), 24.6 (q), 31.6 (q), 35.7 (t), 36.8 (s), 39.2 (s), 39.4 (d), 43.4 (d), 62.7 (t), 63.9 (t), 64.2 (t), 81.3 (d), 111.2 (s); HRMS m/z calcd for $C_{14}H_{24}O_4$ 256.1674, found 256.1676.

3.1.8. (6*S*,11*S*)-11-(Hydroxyethyl)-6,8,8-trimethylspiro[1,3-dioxolane-2,8′-bicyclo[2.2.2]octane]-7-one (19). To a stirred solution of oxalyl chloride (1.3 mL, 15.6 mmol) in dichloromethane (40 mL) was added dimethylsulfoxide (2.2 mL, 31.3 mmol) at −78 °C under nitrogen atmosphere. After being stirred for 10 min, the diol **18** (1.002 g, 3.91 mmol) in dimethylsulfoxide (2 mL) and dichloromethane (20 mL) was added at −78 °C. The stirring was continued for 1.5 h and triethylamine (4.4 mL, 31.3 mmol) was added. After being stirred for 1 h, the reaction was quenched by addition of phosphate buffer (pH 7). The organic layer was separated and the aq layer was extracted with ethyl acetate twice. The combined organic layer was dried over anhyd sodium sulfate and evaporated to dryness to give (6*S*,7*S*)-6,10,10-trimethyl-11-oxospiro[1,3-dioxolane-2,8′-bicyclo[2.2.2]octane]-7-carbaldehyde: $[\alpha]_D^{20}$ −48.7 (c 1.11, $CHCl_3$); IR ($CHCl_3$) 3048, 1721, 1462, 1389, 1350, 1096, 1037, 1013, 951 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.19 (s, 3H), 1.30 (s, 3H), 1.92 (dd, J=15.0, 1.6 Hz, 1H), 2.08 (dd, J=13.6, 2.8 Hz, 1H), 2.23 (d, J=15.0 Hz, 1H), 1.82–2.25 (m, 2H), 2.48 (ddd, J=13.6, 4.2, 2.9 Hz, 1H), 3.85–4.05 (m, 4H), 9.82 (d, J=2.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.5 (q), 20.2 (t), 25.5 (q), 26.0 (q), 41.3 (t), 44.6 (s), 45.8 (d), 46.1 (s), 47.7 (d), 63.2 (t), 64.4 (t), 108.9 (s), 201.9 (d), 217.2 (s); HRMS m/z calcd for $C_{14}H_{20}O_4$ 252.1361, found 252.1359.

To a solution of the crude aldehyde (1.054 g) in ether (50 mL) was added an ethereal solution of methylmagnesium bromide (3.9 mL, 3.0 M, 11.7 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 1.5 h, the reaction was quenched by addition of aq ammonium chloride. The product was extracted with ethyl acetate twice. The combined organic layer was washed with water, brine and dried over anhyd sodium sulfate. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate/*n*-hexane=1:2) of the residue gave an inseparable mixture of two diastereomeric alcohols **19** (940 mg, 90%, colorless oil).

More polar **19**: $[\alpha]_D^{20}$ +0.99 (c 1.00, $CHCl_3$); IR ($CHCl_3$) 3607, 3484, 2990, 2890, 1715, 1462, 1387, 1350, 1097 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.11 (s, 3H), 1.18 (s, 3H), 1.26 (s, 3H), 1.31 (d, J=6.5 Hz, 3H), 1.52–1.68 (m, 1H), 1.75 (dd, J=15.5, 1.4 Hz, 1H), 1.76–2.14 (m, 2H), 2.33 (d, J=15.5 Hz, 1H), 3.82–4.02 (m, 4H), 4.02–4.17 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.6 (q), 21.9 (q), 23.8 (t), 25.9 (q), 26.2 (q), 40.9 (t), 41.1 (d), 43.9 (s), 45.7 (d), 47.5 (s), 63.0 (t), 64.1 (t), 70.3 (d), 109.5 (s), 219.4 (s); HRMS m/z calcd for $C_{15}H_{24}O_4$ 268.1674, found 268.1674.

Less polar **19**: $[\alpha]_D^{20}$ −17.0 (c 1.06, $CHCl_3$); IR ($CHCl_3$) 3500, 2934, 1717, 1462, 1389, 1098, 1010 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.14 (d, J=6.5 Hz, 3H), 1.18 (s, 3H), 1.27 (s, 3H), 1.32–1.48 (m, 1H), 1.74 (dd, J=14.6, 1.2 Hz, 1H), 1.81–2.05 (m, 2H), 2.14 (ddd, J=14.5, 7.1, 2.6 Hz, 1H), 2.54 (d, J=14.6 Hz, 1H), 3.11 (d, J=9.2 Hz, 1H), 3.85–4.05 (m, 4H), 4.41 (ddq, J=9.2, 6.5, 2.6 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.2 (q), 19.5 (t), 22.8 (q), 25.6 (q), 26.2 (q), 40.2 (d), 40.5 (t), 44.2 (s), 46.5 (d), 47.4 (s), 62.9 (t), 64.3 (t), 67.4 (d), 109.6 (s), 219.0 (s); HRMS m/z calcd for $C_{15}H_{24}O_4$ 268.1674, found 268.1673.

3.1.9. (6*S*,11*S*)-11-(Hydroxyethyl)-6,8,8-trimethylspiro[1,3-dioxolane-2,8′-bicyclo[2.2.2]octane]-7-one (20). A mixture of PCC (354 mg, 1.64 mmol), sodium acetate (137 mg, 1.64 mmol), MS-4 Å (120 mg, powder), and Celite (100 mg) was evacuated at rt for 1 h. To the mixture was added dichloromethane (3 mL) and then a solution of the alcohol **19** (219 mg, 0.82 mmol) in dichloromethane (7 mL) was added successively under nitrogen atmosphere. After being stirred for 30 min, the slurry was passed through silica-gel short column. Evaporation of the solvent followed by medium pressure LC purification of the residue (eluent: ethyl acetate/*n*-hexane=1:1) provided the ketone **20** (213 mg, 98%, colorless oil): $[\alpha]_D^{20}$ +26.1 (c 1.03, $CHCl_3$); IR ($CHCl_3$) 3040, 2363, 1713, 1357, 1096, 1013 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03 (s, 3H), 1.20 (s, 3H), 1.29 (s, 3H), 1.69 (dd, J=15.3, 1.6 Hz, 1H), 1.86 (t, J=2.9 Hz, 1H), 2.17 (s, 3H), 2.05–2.30 (m, 1H), 2.55 (dd, J=11.6, 7.0 Hz, 1H), 2.73 (d, J=15.3 Hz, 1H), 3.80–4.05 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 17.3 (q), 23.5 (t), 25.8 (q), 26.1 (q), 31.0 (q), 39.7 (t), 44.1 (s), 45.9 (d), 46.6 (d), 63.1 (t), 64.1 (t), 109.1 (s), 207.6 (s), 217.9 (s); HRMS m/z calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1518.

3.1.10. (6*S*,11*R*)-11-(Hydroxyethyl)-6,8,8-trimethylspiro[1,3-dioxolane-2,8′-bicyclo[2.2.2]octane]-7-one (21). A solution of the *endo*-methylketone **20** (58 mg, 0.22 mmol) and potassium hydroxide (50 μL, 2.2 M solution in ethanol, 0.11 mmol) in ethanol (7 mL) was heated at reflux for 19 h under nitrogen atmosphere. The reaction was quenched by addition of aq ammonium chloride. The product was extracted with ethyl acetate twice and the combined organic layer was washed with water, brine and dried over anhyd sodium sulfate. Evaporation of the solvent followed by medium pressure LC (eluent: ethyl acetate/*n*-hexane=1:1) gave the *exo*-methylketone **21** (47 mg, 81%, colorless crystals) along with recovered *endo*-methylketone **20** (7 mg, 12%).

exo-Methylketone **21**: mp 80–82 °C; $[\alpha]_D^{20}$ −60.3 (c 1.02, $CHCl_3$); IR ($CHCl_3$) 2980, 2930, 2882, 1730, 1549, 1354, 1099, 796 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.95 (s, 3H), 1.22 (s, 3H), 1.27 (s, 3H), 1.73–1.95 (m, 4H), 2.16 (s,

3H), 2.33 (ddd, J=14, 11, 4 Hz, 1H), 3.05 (dd, J=11, 7 Hz, 1H), 3.85–4.04 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.0 (q), 23.8 (t), 24.8 (q), 26.9 (q), 31.7 (q), 44.7 (s), 45.7 (d), 45.8 (t), 46.4 (s), 52.5 (d), 63.0 (t), 64.2 (t), 109.2 (s), 210.7 (s), 217.2 (s). Anal. Calcd for $C_{15}H_{22}O_4$: C, 67.65; H, 8.33. Found: C, 67.24; H, 8.45.

3.1.11. 11-((1*R*)-1-Hydroxy-1-methylprop-2-enyl)(6*S*,11*R*)-6,8,8-trimethylspiro[1,3-dioxolane-2,8′-bicyclo[2.2.2]octane]-7-one (24a) and 11-((1*S*)-1-hydroxy-1-methylprop-2-enyl)(6*S*,11*R*)-6,8,8-trimethylspiro[1,3-dioxolane-2,8′-bicyclo[2.2.2]octane]-7-one (24b). To a stirred solution of vinylmagnesium chloride (2.3 mL, 1.32 M solution in THF, 3.1 mmol) in THF (3 mL) was added a solution of methylketone **21** (163 mg, 0.61 mmol) in THF (3 mL) at −30 °C under nitrogen atmosphere. After being stirred for 3 h to −20 °C, the reaction was quenched by addition of aq ammonium chloride. After extraction with ethyl acetate, the combined organic layer was washed with water, brine and dried over anhyd sodium sulfate. After evaporation of the solvent, the residue was purified by medium pressure LC (eluent: ethyl acetate/*n*-hexane=1:1) to give two diastereomers, less polar alcohol **24b** (40 mg, 22%, colorless crystals) and more polar alcohol **24a** (105 mg, 58%, colorless crystals).

Less polar **24b**: mp 86–88 °C; $[\alpha]_D^{20}$ −63.7 (c 1.23, $CHCl_3$); IR ($CHCl_3$) 3584, 2980, 2934, 2882, 1714, 1454, 1386, 1197, 1153, 1097, 1037, 918, 775 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 3H), 1.18 (s, 3H), 1.21 (s, 3H), 1.22 (s, 3H), 1.68–2.21 (m, 6H), 3.86–4.02 (m, 4H), 5.00 (dd, J=10.7, 1.0 Hz, 1H), 5.19 (dd, J=17, 1.0 Hz, 1H), 6.01 (dd, J=17, 10.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.0 (q), 23.6 (t), 24.5 (q), 27.1 (q), 27.2 (q), 48.2 (s), 45.5 (d), 47.9 (t), 48.6 (s), 49.6 (d), 63.1 (t), 64.1 (t), 76.1 (s), 109.4 (s), 111.0 (t), 146.7 (d), 222.0 (s). Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.91. Found: C, 69.43; H, 8.94.

More polar **24a**: mp 87–89 °C; $[\alpha]_D^{20}$ −51.2 (c 1.10, $CHCl_3$); IR ($CHCl_3$) 3611, 2976, 1720, 1477, 1386, 1196, 1140, 1097, 1035, 927 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.16 (s, 3H), 1.21 (s, 3H), 1.28 (s, 3H), 1.39–2.21 (m, 6H), 3.86–4.02 (m, 4H), 5.07 (dd, J=10.7, 1.3 Hz, 1H), 5.18 (dd, J=17.3, 1.3 Hz, 1H), 5.85 (dd, J=17.3, 10.7 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.3 (q), 24.3 (t), 24.5 (q), 26.9 (q), 27.6 (q), 45.0 (s), 45.5 (d), 48.3 (t), 48.5 (s), 49.6 (d), 49.6 (s), 63.1 (t), 64.1 (t), 109.4 (s), 113.7 (t), 142.4 (d), 220.8 (s); HRMS m/z calcd for $C_{17}H_{26}O_4$ 294.1831, found 294.1832.

3.1.12. 11-[(1*R*)-1-(Methoxymethoxy)-1-methylprop-2-enyl](6*S*,11*R*)-6,8,8-trimethylspiro[1,3-dioxolane-2,8′-bicyclo[2.2.2]octane]-7-one (25a). To a solution of the allylalcohol **24a** (130 mg, 0.44 mmol) in DMF (2 mL) were added diisopropylethylamine (465 μL, 2.67 mmol) and chloromethylmethyl ether (170 μL, 2.23 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 6 h at 60 °C, the reaction was quenched by addition of water. The product was extracted with ethyl acetate twice. The combined organic layer was washed with water, brine and dried over anhyd sodium sulfate. Evaporation of the solvent followed by purification by medium pressure LC (eluent: ethyl acetate/*n*-hexane=1:1) gave the allylether **25a** (133 mg, 89%, colorless oil): $[\alpha]_D^{20}$ −85.1 (c 1.24, $CHCl_3$); IR ($CHCl_3$) 2982, 1718, 1141, 1097, 1084, 1064, 1024, 929, 761, 744 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 (s, 3H), 1.14 (s, 3H), 1.20 (s, 3H), 1.27 (s, 3H), 1.35–2.30 (m, 6H), 3.08 (s, 3H), 3.83–4.00 (m, 4H), 4.48 (d, J=7.0 Hz, 1H), 4.65 (d, J=7.0 Hz, 1H), 5.16 (dd, J=17, 1.4 Hz, 1H), 5.24 (dd, J=11, 1.4 Hz, 1H), 5.73 (dd, J=17, 11 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.4 (q), 21.3 (q), 23.8 (t), 24.6 (q), 27.7 (q), 45.1 (s), 45.6 (d), 48.5 (t), 48.8 (s), 49.7 (d), 56.7 (q), 63.1 (t), 64.1 (t), 82.6 (s), 91.4 (t), 109.5 (s), 117.9 (t), 139.9 (d), 221.0 (s); HRMS m/z calcd for $C_{19}H_{30}O_5$ 338.2093, found 338.2089.

3.1.13. 11-[(1*S*)-1-(Methoxymethoxy)-1-methylprop-2-enyl](6*S*,11*R*)-6,8,8-trimethylspiro[1,3-dioxolane-2,8′-bicyclo[2.2.2]octane]-7-one (25b). To a solution of the allylalcohol **24b** (52 mg, 0.18 mmol) in DMF (1 mL) were added diisopropylethylamine (185 μL, 1.07 mmol) and chloromethylmethyl ether (67 μL, 0.89 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 6 h at 60 °C, the reaction was quenched by addition of water. The product was extracted with ethyl acetate twice. The combined organic layer was washed with water, brine and dried over anhyd sodium sulfate. Evaporation of the solvent followed by purification by medium pressure LC (eluent: ethyl acetate/*n*-hexane=1:1) gave the allylether **25b** (57 mg, 95%, colorless oil): $[\alpha]_D^{20}$ −35.1 (c 1.13, $CHCl_3$); IR ($CHCl_3$) 2978, 2885, 1720, 1454, 1412, 1346, 1180, 972, 951, 927 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.16 (s, 3H), 1.18 (s, 3H), 1.22 (s, 3H), 1.20–2.23 (m, 6H), 3.36 (s, 3H), 3.82–4.00 (m, 4H), 4.51 (d, J=7 Hz, 1H), 4.63 (d, J=7 Hz, 1H), 5.07 (dd, J=18, 1 Hz, 1H), 5.16 (dd, J=11, 1 Hz, 1H), 5.77 (dd, J=18, 11 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.1 (q), 20.5 (q), 24.3 (t), 24.5 (q), 27.7 (q), 45.0 (s), 45.5 (d), 48.4 (t), 48.6 (s), 49.0 (d), 56.0 (q), 63.1 (t), 64.1 (t), 82.0 (s), 91.6 (t), 109.5 (s), 115.1 (t), 142.8 (d), 220.7 (s); HRMS m/z calcd for $C_{19}H_{30}O_5$ 338.2093, found 338.2089.

3.1.14. (12*S*,13*S*)-7,7,11,13-Tetramethylspiro[1,3-dioxolane-2,10′-tricyclo[5.3.1.0^{3,8}]undecane]-10-en-8-ol (9). A mixture of sodium (24 mg, 1.04 mmol) and naphthalene (91 mg, 0.71 mmol) in THF (2.5 mL) was stirred vigorously at −55 °C to rt under nitrogen atmosphere, when the color developed dark green. After being cooled again at −55 °C for 10 min, a solution of the allylether **25a** (40 mg, 0.12 mmol) in THF (2.5 mL) was added. Stirring was continued for 2.5 h maintaining the color dark green. The reaction was quenched by addition of aq ammonium chloride. The product was extracted with ethyl acetate twice and the combined organic layer was washed with water, brine and dried over anhyd sodium sulfate. Evaporation of the solvent followed by medium pressure LC purification (eluent: ethyl acetate/*n*-hexane=1:1) gave tricyclic alkene **9** (31 mg, 95%, colorless solid): mp 123 °C; $[\alpha]_D^{20}$ +29.8 (c 1.31, $CHCl_3$); IR ($CHCl_3$) 2964, 2930, 2363, 1726, 1450, 1091, 1064, 758 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (s, 3H), 1.12 (s, 3H), 1.24 (s, 3H), 1.27 (s, 3H), 1.25–1.61 (m, 3H), 1.61–1.65 (m, 3H), 1.67–2.40 (m, 5H), 3.75–4.05 (m, 4H), 5.10–5.20 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.6 (q), 22.2 (q), 25.6 (t), 26.6 (q), 28.2 (q), 35.2 (t), 38.5 (s), 40.5 (s), 41.7 (t), 42.8 (d), 45.6 (d), 62.5 (t), 63.9 (t), 74.0

(s), 110.7 (s), 118.5 (d), 138.6 (s); HRMS *m/z* calcd for $C_{17}H_{26}O_3$ 278.1882, found 278.1877.

3.1.15. (12*S*,9*R*,10*R*,11*R*)-10-(Methoxymethoxy)-7,7,9,10,12-pentamethylspiro[1,3-dioxolane-2,9′-tricyclo[4.3.1.0^{3,7}]decane]-8-ol (27). A mixture of lithium (19 mg, 0.8 mmol) and naphthalene (118 mg, 0.92 mmol) in THF (4 mL) and 1,4-dioxane (1.5 mL) was stirred vigorously at −55 °C to 0 °C under nitrogen atmosphere, when the color developed dark green. After being cooled again at −55 °C, a solution of the allylether **25b** (52 mg, 0.16 mmol) in THF (2 mL) and 1,4-dioxane (2 mL) was added. Stirring was continued for 3 h maintaining the color dark green. The reaction was quenched by addition of aq ammonium chloride. The product was extracted with ethyl acetate twice. The combined organic layer was washed with water, brine and dried over anhyd sodium sulfate. Evaporation of the solvent followed by medium pressure LC purification (eluent: ethyl acetate/*n*-hexane=3:5) gave 6-*endo-trig* tricyclic alkene **9** (23 mg, 54%, colorless oil) along with 5-*exo-trig* product **27** (15 mg, 29%, colorless oil).

5-*exo-trig* Product **27**: IR ($CHCl_3$) 3632, 2936, 1730, 1462, 1389, 1146, 1086, 1028 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (s, 3H), 1.03 (d, *J*=8.0 Hz, 3H), 1.04 (s, 3H), 1.15 (s, 3H), 1.19 (t, *J*=2.5 Hz, 1H), 1.44 (s, 3H), 1.57 (dd, *J*=15.0, 1.0 Hz, 1H), 1.74 (dd, *J*=10.5, 2.5 Hz, 1H), 1.92 (ddd, *J*=14.5, 10.5, 2.5 Hz, 1H), 1.97 (d, *J*=15.0 Hz, 1H), 2.20 (dt, *J*=14.5, 2.5 Hz, 1H), 2.55 (q, *J*=8.0 Hz, 1H), 3.40 (s, 3H), 3.87–4.99 (m, 4H), 4.59 (d, *J*=7.0 Hz, 1H), 4.67 (d, *J*=7.0 Hz, 1H), 4.59 (d, *J*=7.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.1 (q), 21.2 (t), 23.5 (q), 24.1 (q), 26.5 (q), 27.3 (q), 41.6 (d), 42.7 (s), 44.8 (d), 45.8 (s), 47.1 (d), 48.6 (d), 55.7 (q), 62.4 (t), 63.8 (t), 81.3 (s), 84.1 (s), 92.1 (t), 109.9 (s); HRMS *m/z* calcd for $C_{19}H_{32}O_5$ 340.2250, found 340.2253.

3.1.16. (6*S*,7*S*,8*S*)-3-Hydroxy-2,2,6,8-tetramethyltricyclo[5.3.1.0^{3,8}]undecan-10-one (valerianananoid A 1). To a solution of the tricyclic alkene **9** (231 mg, 0.83 mmol) in ethyl acetate (2 mL) was added palladium on carbon (165 mg, 5% Pd wet) and the system was purged with hydrogen. After being stirred for 210 h at rt, the suspension was passed through silica-gel short column and the solvent was evaporated to dryness.

To a solution of the residue in water (1 mL) and THF (1 mL), *p*-toluenesulfonic acid (2 mg, 0.015 mmol) was added. After being stirred for 20 min at rt, the reaction was quenched by addition of aq sodium hydrogen carbonate. The product was extracted with ethyl acetate. The combined organic layer was washed with water, brine and dried over anhyd sodium sulfate. Evaporation of the solvent followed by medium pressure LC purification (eluent: ethyl acetate/*n*-hexane=2:3) gave valerianananoid A **1** (177 mg, 90% in two steps): mp 123–124 °C (lit.[4] 122–124 °C; lit.[9] 117–118 °C); $[\alpha]_D^{20}$ −82.3 (*c* 0.27, $CHCl_3$) {lit.[4] −34.6 (*c* 0.231, $CHCl_3$); lit.[9] −33.3 (*c* 0.3, $CHCl_3$)}; IR ($CHCl_3$) 3440, 1720, 1470, 1390, 1340, 1220, 1100, 1070, 1050, 1000, 890, 590 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (d, *J*=6.7 Hz, 3H), 0.98 (s, 3H), 1.02 (s, 3H), 1.18 (s, 3H), 1.38–1.50 (m, 2H), 1.50–1.58 (m, 2H), 1.62 (m, 1H), 1.74 (m, 1H), 1.78 (d, *J*=19 Hz, 1H), 1.85 (dd, *J*=11.9, 5.5 Hz, 1H), 1.90 (t like, 1H), 2.04 (m, 1H), 2.64 (d, *J*=19 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.7 (q), 19.5 (q), 20.9 (q), 23.0 (q), 27.7 (q), 27.9 (d), 28.3 (t), 33.1 (t), 40.5 (s), 42.4 (d), 43.6 (d), 46.5 (t), 57.7 (d), 74.3 (s), 216.1 (s). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.53; H, 10.24.

3.1.17. (6*S*,7*S*,8*S*,10*R*)-2,2,6,8-Tetramethyltricyclo-[5.3.1.0^{3,8}]undecane-3,10-diol (valerianananoid B 2). To a solution of valerianananoid A **1** (177 mg, 0.75 mmol) was added in methanol (10 mL) sodium borohydride (573 mg, 15.1 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 12 h at rt, the reaction was quenched by addition of aq ammonium chloride. The product was extracted with ethyl acetate twice. The combined organic layer was washed with water, brine and dried over anhyd sodium sulfate. Evaporation of the solvent followed by column chromatography (eluent: ethyl acetate/*n*-hexane=1:8 to 1:1) gave valerianananoid B **2** (177 mg, 99%): mp 171 °C decomposition (lit.[1] 133–135 °C; lit.[4] 200–202 °C; lit.[5] 179–181 °C; lit.[9] 185–187 °C); $[\alpha]_D^{24}$ −117.7 (*c* 0.69, $CHCl_3$) {lit.[1] −115.8 (*c* 0.41, MeOH); lit.[4] −57.87 (*c* 0.197, $CHCl_3$); lit.[5] −75.4 (*c* 1.1, $CHCl_3$); lit.[9] −90.0 (*c* 1.0, $CHCl_3$)}; IR ($CHCl_3$) 3665, 3455, 1728, 1601, 1463, 909 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.80 (d, *J*=6.8 Hz, 3H), 0.90 (s, 3H), 1.12 (s, 3H), 1.24 (s, 3H), 1.60 (dd, *J*=13.8, 10.3 Hz, 1H), 1.20–1.80 (m, 10H), 1.88 (dd, *J*=13.8, 7.8 Hz, 1H), 1.90–2.00 (m, 1H), 3.92 (br t, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.9, 20.2, 24.2, 25.5, 27.7, 28.2, 28.6, 32.6, 39.4, 39.5, 40.4, 42.5, 46.8, 72.5, 75.1; HRMS *m/z* calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.1934.

3.1.18. (6*S*,7*S*,8*S*,10*R*)-3-Hydroxy-2,2,6,8-tetramethyltricyclo[5.3.1.0^{3,8}]undec-10-yl acetate (valerianananoid C 3). To a solution of valerianananoid B **2** (105 mg, 0.44 mmol) and DMAP (26 mg, 0.21 mmol) in dichloromethane (5 mL) were added pyridine (430 μL, 5.32 mmol) and acetic anhydride (415 μL, 4.39 mmol) at 0 °C under nitrogen atmosphere. After being stirred for 3 h, the reaction was quenched by addition of water. The product was extracted with ethyl acetate twice. The combined organic layer was washed with water, brine and dried over anhyd sodium sulfate. Evaporation followed by medium pressure LC purification (eluent: ethyl acetate/*n*-hexane=1:3) gave valerianananoid C **3** (123 mg, 100%): mp 84 °C (lit.[1] 85–86 °C; lit.[4] 79–80 °C; lit.[9] 74–76 °C); $[\alpha]_D^{24}$ −109.8 (*c* 0.37, $CHCl_3$) {lit.[1] −114.8 (*c* 3.3, $CHCl_3$); lit.[4] −56.88 (*c* 0.16, $CHCl_3$); lit.[5] −77.3 (*c* 1.1, $CHCl_3$); lit.[9] −116.0 (*c* 1.0, $CHCl_3$)}; IR ($CHCl_3$) 3603, 3117, 2957, 1723, 1464, 1368, 1265 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.80 (d, *J*=6.5 Hz, 3H), 0.90 (s, 3H), 1.10 (s, 3H), 1.15 (s, 3H), 1.20–1.80 (m, 7H), 1.37 (ddd, *J*=10.0, 6.5, 3.0 Hz, 1H), 1.44 (dd, *J*=14.0, 1.9 Hz, 1H), 1.90–2.04 (m, 1H), 1.96 (dd, *J*=14.0, 7.8 Hz, 1H), 2.02 (s, 3H), 4.80 (ddd, *J*=10.0, 7.8, 1.9 Hz, 1H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 18.8, 20.0, 21.7, 23.6, 25.1, 27.7, 27.9, 28.6, 32.7, 36.0, 39.1, 40.1, 42.5, 43.3, 74.5, 75.0, 170.6; HRMS *m/z* calcd for $C_{17}H_{28}O_3$ 280.2038, found 280.2032.

3.2. Crystallographic data of 11 (23 °C)

Colorless crystals (from *n*-hexane); formula $C_{28}H_{38}O_4$, fw=438.61; monoclinic, space group $P2_1$ (no. 4),

a=9.309(3) Å, b=10.200(7) Å, c=13.450(3) Å; β=91.47(2)°; V=1276.6(8) Å^3, Z=2, D_{calcd}=1.141 g/cm^3, μ(Mo Kα)=0.90 mm^{-1}. A total of 3281 reflections, 1931 ($I>3.00\sigma(I)$) were used in refinement: R=0.051, R_w=0.048. The reflection intensities were collected on a Rigaku AFC7S diffractometer with a rotating anode (50 kV, 30 mA) using graphite monochromated Mo Kα (λ=0.7107 Å).

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