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Determination of the absolute configuration of vibsanin F by asymmetric synthesis via π-allylpalladium complex

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Abstract—The absolute configuration of vibsanin F (**1**), one of the simplest 11-membered ring vibsane-type diterpene, was established to be 6*R*, 7*S* and 11*S* by asymmetric synthesis. A diastereomer (**1a**) with a 6*S*, 7*S* and 11*S* configuration was synthesized starting from myrcene by procedures featuring a Sharpless asymmetric epoxidation and a high diastereoselective eleven-membered ring formation between a π-allylpalladium complex and a β-ketoester nucleophile. Subsequent reduction of epoxide in **1a** with $LiAlH_4$ gave a diol, which was identical with that derived from vibsanin F.

Vibsane-type diterpenes, vibsanins A–F, were first isolated from the leaves of *Viburnum awabuki* by Kawazu[1] in 1980. Although these diterpenes comprised unprecedented carbon skeletons, the proposed plane structures of them had not been refined on except for vibsanin E for a decade.[2] In 1997, we established the absolute configuration of vibsanin B (**2**) on the basis of the chemical conversion of a seven-membered ring version, vibsanin C, the absolute structure of which was determined by X-ray crystallographic analysis.[3] Since then, we have continued chemical studies on this type of diterpenes occurring in Viburnum species. As results, a variety of vibsane-type diterpenes have been isolated, thereby dividing into further three subtypes such as eleven-membered, seven-membered,[4] and rearranged ones.[5] Additionally, many of them show interesting biological activities, e.g. piscicidial, plant growth inhibitory,[1] and cytotoxic activity.[5] However, no effort on synthesis of vibsane-type diterpenes has been made in spite of novel structures with significant biological activities. Hence, we have initiated stereoselective synthesis of the simplest vibsane-type diterpene, vibsanin F (**1**),[1] the relative and absolute stereochemistry for which has remained unsolved. Vibsanin F (**1**) has three chiral centers which are tentatively assignable as 6*S*, 7*S* and 11*S* (**1a**) or 6*R*, 7*S* and 11*S* (**1b**) according to the 7*R* and 11*S* chirality of vibsanin B (**2**).[3] Our first effort has been directed on asymmetric synthesis of **1a** (Fig. 1).

Our synthetic plan for **1a** is outlined in Figure 2. Commercially available myrcene would be converted to diepoxide **3** by asymmetric epoxidation using a Sharpless method[6] followed by regioselective epoxidation on exomethylene. Diepoxide **3** would be coupled with a

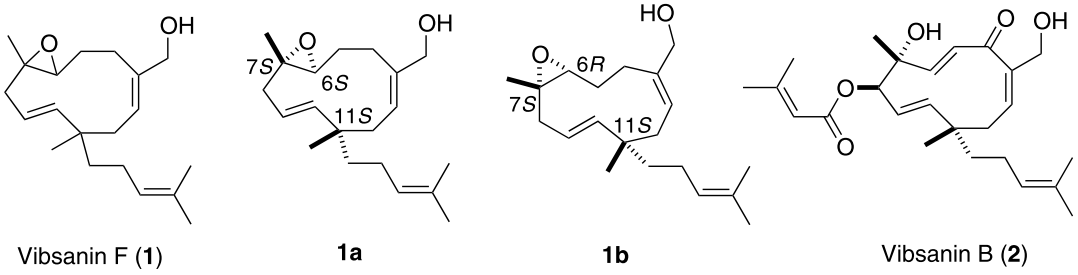

Figure 1. Possible structures **1a** and **1b** of vibsanin F (**1**).

Keywords: vibsanin F; vibsane-type diterpene; absolute configuration; π-allylpalladium complex.
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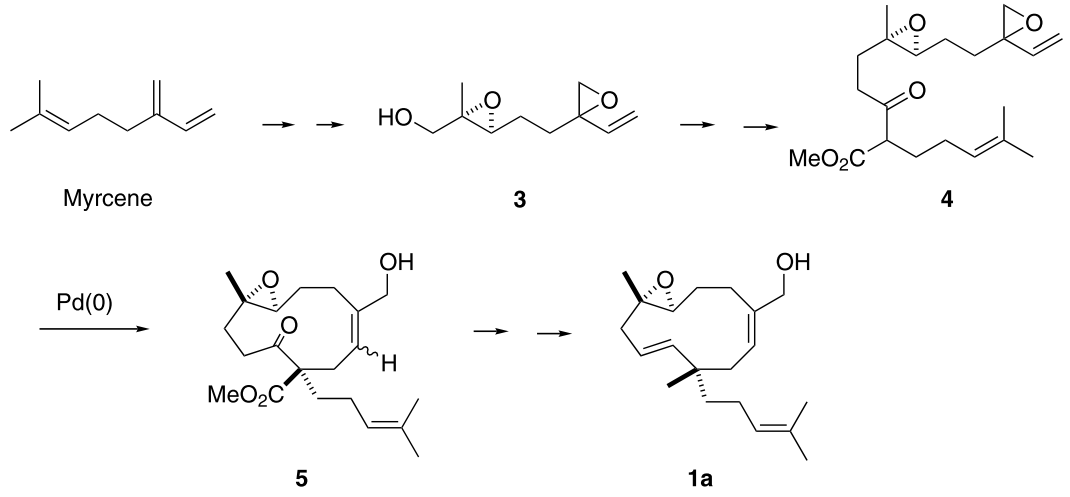
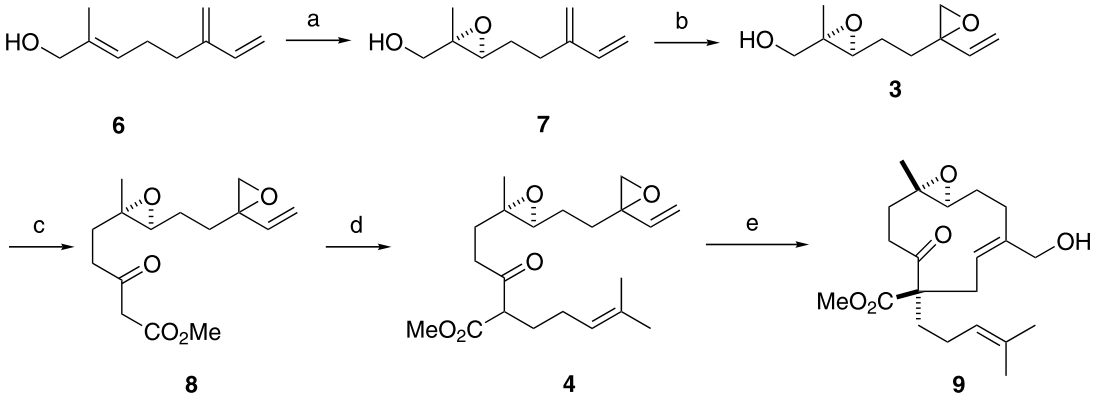


Figure 2. Synthetic plan of **1a** via a π-allylpalladium complex.

dianion of methyl acetoacetate[7] to give **4**. Stereoselective macrocyclization via π-allylpalladium complex[8] would be employed for **4**, with expectation that eleven-membered ring formation could be diastereoselctively made to give **5**, which would in turn lead to **1a** after several functionalizations.

The synthesis of **1a** began with the allyl alcohol **6** readily available from myrcene.[9] Asymmetric epoxidation of **6** by Sharpless method[6] provided epoxide **7** in 99% yield with 92% ee, determined by ^{1}H NMR analysis of the corresponding Mosher ester derivative.[10] Regioselective epoxidation of **7** with *m*-chloroperbenzoic acid gave exclusively diepoxide **3** as a diastereomeric mixture in 91% yield. The displacement of mesylate and tosylate of the primary hydroxyl group in **3** with the dianion of methyl acetoacetate did not proceed at all. Therefore, triflate was used as a more effective leaving group, but it was found to be too liable to be isolated. As a result, large excess (5.0 equiv.) of the dianion of methyl acetoacetate[7] was slowly added at 0°C to in situ prepared triflate of **3** to afford compound **8** with an acetoacetate unit in 94% yield. Introduction of a 4-methyl-3-pentenyl unit was achieved in 77% yield by using sodium hydride and 15-crown-5 as an additive in DMSO, giving rise to the precursor **4** needed for a subsequent palladium-catalyzed macrocyclization (Scheme 1).

Next, our attention was directed toward palladium-catalyzed macrocyclization of the vinyl epxoide **4** through π-allylpalladium complex.[8] Crucial cyclization of the vinyl epoxide proceeded stereoselectively to afford a sole product **9** in 45% yield when 10 mol% $Pd(PPh_3)_4$ was used as the catalyst in THF. Switching the palladium-catalyst did not improve the formation of an eleven-membered ring, but recovered mostly **4**. The macrocyclization of **4** to **9** was examined under a catalytic system of 10 mol% $Pd(PPh_3)_4$ in a variety of solvent at 0.01M concentration. As results, the use of DMSO as solvent greatly enhanced this stereoslective cyclization to give rise to **9**[11] in 60% yield. The stereoselective formation of **9** can be explained by assuming that transition states **A** and **B**, as shown in Figure 3,



Scheme 1. *Reagents and conditions*: (a) $Ti(OiPr)_4$, L-(+)-DET, TBHP, MS 4 Å, CH_2Cl_2, −35°C, 99% (92% ee); (b) *m*CPBA, CH_2Cl_2, 0°C, 91%; (c) Tf_2O, Et_3N, THF, −78°C, then 5 equiv. the dianion of methyl acetoacetate generated with NaH and *n*BuLi, THF, 0°C, 94%; (d) NaH, 15-crown-5, DMSO, then 5-iodo-2-methylpent-2-ene, 77%; (e) 10 mol% $Pd(PPh_3)_4$, DMSO, 90°C, 60%.

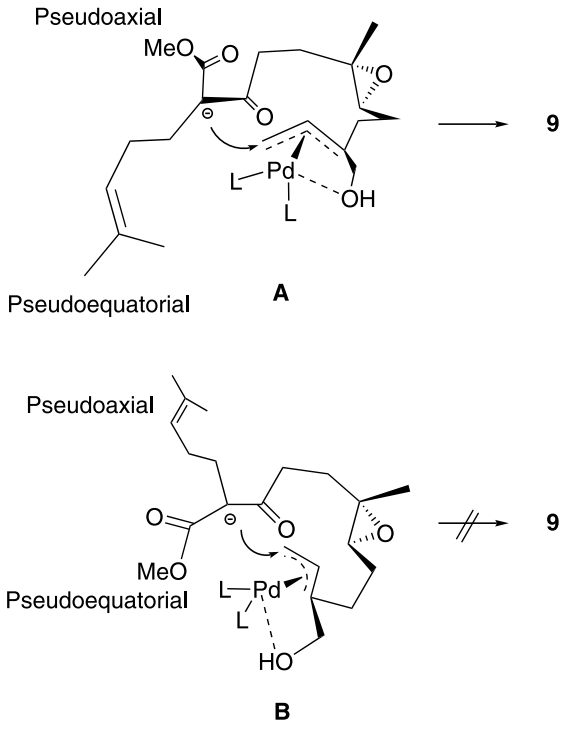


Figure 3. Possible transition states **A** and **B** for palladium-catalyzed cyclization of **4**.

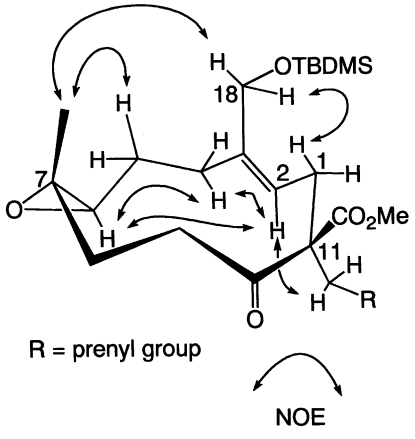


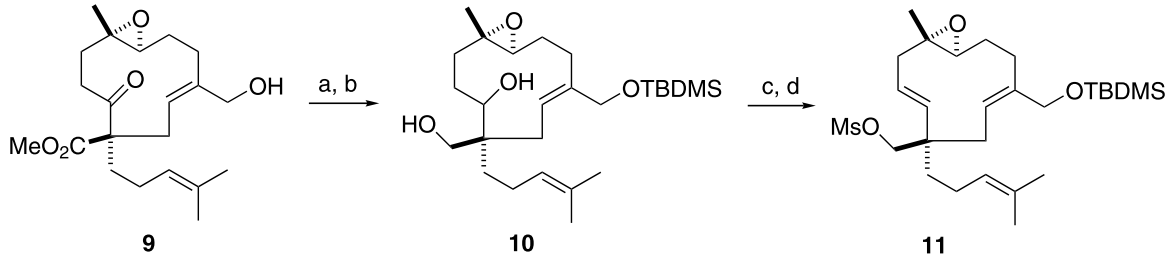
Figure 4. Most stable conformation of **9a** obtained by MM2 calculation and representative NOE.

would be involved in this cyclization. Namely, the chelation between the palladium and the allyl alcohol formed by Pd(0) oxidative addition of the vinyl epoxide predominately leads to the formation of a *Z*-olefin. If a nucleophilc displacement at the π-allylpalladium intermediate with the anion of the β-keteoester moiety proceeds through a product-like transition state, transition state **A**, which should lead to more stable compound **9** with a pseudoequatrial C-6 unit and a pseudoaxial methyl ester group, favors over transition state **B** bringing into less stable product with the opposite stereochemistry at the quaternary center.

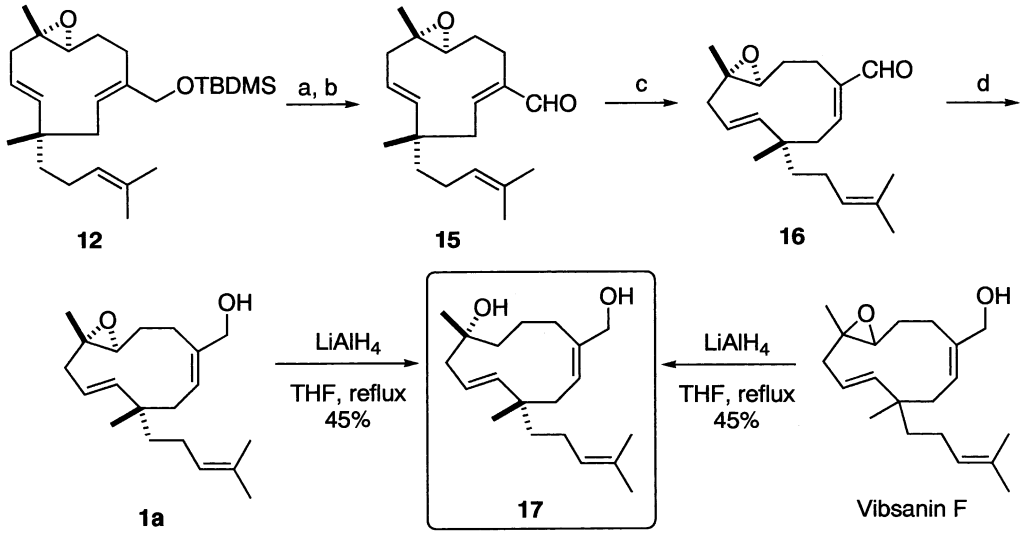
Although the eleven-membered ring was diastereoselectively constructed, the *Z*-geometry of the trisubstituted olefin in **9** has to be converted to an *E* form which is essential for vibsanin F. MM2 calculations of vibsanin F related compounds were performed by using Macromodel®, thereby indicating that aldehyde **15** (shown in Scheme 3) with a *Z*-double bond is less stable by 7 kJ mol^{-1} than aldehyde **16** with an *E*-double bond. This result encouraged us to attempt isomerization of the *Z*-olefin into the desirable *E*-olefin at a later stage after **9** is converted to the corresponding aldehyde **15**. First, the alcohol **9** was protected with TBDMSCl, followed by reduction of both the carbonyl groups with $LiAlH_4$ to give rise to the diol **10** without touching the epxoide moiety, which was then mesylated. The resultant dimesylate **10a** was subjected to elimination of the secondary mesylate under standard conditions, giving rise to monomesylate **11** in 60% yield over three steps (Scheme 2).

Subsequent reductive demesylation of **11** to generate a methyl group was troublesome. As shown in Table 1, neither of Zn nor $NaBH_3CN$ gave the desired compound **12** but a ring expanded product **14** (entry 3 and 5), whereas $LiAlH_4$ reduction afforded solely an alcohol **13** in good yield (entry 2). After numerous trails, it was pleased to find that reductive demesylation of **11** nicely proceeded with $NaBH_4$ in aprotic polar solvent[12] to give the desirable product **12**. Particularly, a system of $NaBH_4$–DMPU at 55°C reduced selectively the mesylate moiety of **11**, resulting in the formation of **12** in 81% yield.

After deprotection of the silylether in **12** with TBAF, the obtained hydroxyl group was oxidized with Dess–Martin periodinane[13] to yield aldehyde **15** quantitatively. Isomerization of the *Z*-olefin in **15** into the *E*-olefin was effected under radical conditions with

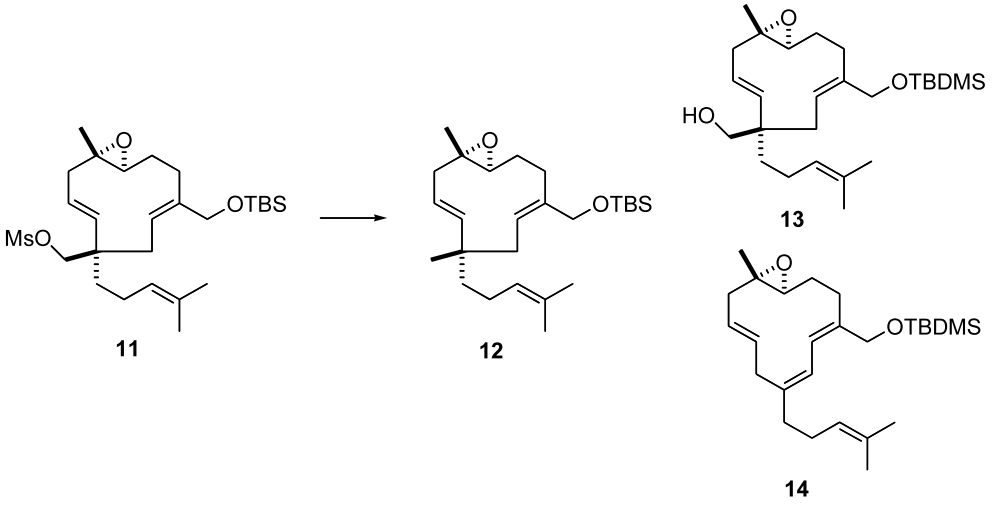


Scheme 2. *Reagents and conditions*: (a) TBDMSCl, Et_3N, 4-DMAP, CH_2Cl_2, 74%; (b) $LiAlH_4$, THF, 0°C; (c) MsCl, Et_3N, 4-DMAP, CH_2Cl_2, 0°C; (d) DBU, toluene, 120°C, 60% over three steps.



Scheme 3. *Reagents and conditions*: (a) TBAF, THF, 100%; (b) Dess–Martin, Et_3N, CH_2Cl_2, 100%; (c) PhSH, AIBN, benzene, 90°C, 48%; (d) $NaBH_4$, $CeCl_3$, MeOH, 0°C, 56%.

Table 1. Reductive conversion of mesylate **11** to **12**



Entry	Reductive conditions[a]	Product (%)		
		12	**13**	**14**
1[b]	Super hydride, THF, reflux	–	–	–
2	$LiAlH_4$, THF, reflux	–	80	–
3	Zn, NaI, HMPA, 110°C	–	–	23
4[b]	Super hydride, DMSO, 55°C	–	–	–
5	$NaBH_3CN$, DMSO, 55°C	–	–	87
6[c]	$NaBH_4$, DMSO, 55°C	69	–	–
7[d]	$NaBH_4$, DMPU, 55°C	81	–	–
8	$NaBH_4$, HMPA, 55°C	70	–	–

[a] Excess reagents were used.
[b] No reaction.
[c] **11** (21%) was recovered.
[d] **11** (13%) was recovered.

AIBN and thiophenol[14] to bring into the *E*-olefin **16** in 48% yield. Finally, a conjugated aldehyde group in **16** was reduced by the Luche protocol[15] to afford **1a**.[16] The ^{1}H NMR of **1a**, however, was not identical with that of natural vibsanin F.

Thus, each epoxide ring of synthetic product **1a** and vibsanin F was reduced with $LiAlH_4$, resulting in the preparation of the same diol **17**.[17] ^{1}H NMR and specific rotation for the both diols derived from synthetic **1a** and natural vibsanin F were identical to each other (synthetic **17**: $[\alpha]_D$+33.4°, natural **17**: $[\alpha]_D$+32.7°).

In conclusion, we succeeded in the asymmetric synthesis of one (**1a**) of two possible structures for vibsanin F by applying palladium-catalyzed macrocyclization to the vinyl epoxide and the β-keteoester coexisting in a molecule, and thereby could propose the correct absolute configuration of vibsanin F to be **1b** with a 6*R*, 7*S* and 11*S* configuration. Synthesis of the correct structure of vibsanin F is currently ongoing.

Acknowledgements

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16. **1a**: $[\alpha]_D^{19}$+46.0° (*c* 0.12, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (3H, s), 1.31 (3H, s), 1.59 (3H, s), 1.68 (3H, s), 2.54 (1H, dd, J=4.9, 12.0 Hz), 2.69 (1H, dd, J=3.0, 11.0 Hz), 2.73 (1H, dd, J=3.0, 9.6 Hz), 3.96 (1H, d, J=12.6 Hz), 4.30 (1H, d, J=12.6 Hz), 5.10 (1H, brt, J=7.1 Hz), 5.43 (1H, d, J=16.2 Hz), 5.53 (1H, ddd, J=4.9, 8.5, 16.2 Hz), 5.69 (1H, dd, J=3.8, 11.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.4, 17.6, 23.3, 23.4, 23.9, 24.4, 25.7, 39.1, 40.0, 41.5, 43.5, 62.1, 64.2, 66.5, 122.3, 124.4, 131.3, 138.5, 142.5, 145.3. IR (film): 3427, 2964, 1069 cm^{-1}. FABMS *m*/*z* (rel. int.) 327 $[M+Na]^+$, 136 (100). HRFABMS *m*/*z*: 327.2293 $[M+Na]^+$; Calcd 327.2300 for $C_{20}H_{32}O_2Na$.
17. **17**: $[\alpha]_D^{21}$+33.4° (*c* 0.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (3H, s), 1.21 (3H, s), 1.60 (3H, s), 1.69 (3H, d, J=1.1 Hz), 2.23 (1H, d, J=6.0 Hz), 2.23 (1H, d, J=6.0 Hz), 3.97 (2H, brs), 5.12 (1H, ddq, J=1.1, 7.1, 7.1 Hz), 5.26 (1H, ddd, J=6.6, 6.6, 15.9 Hz), 5.30 (1H, d, J=15.9 Hz), 5.54 (1H, t, J=8.5 Hz).