Published in final edited form as:
Angew Chem Int Ed Engl. 2009 ; 48(31): 5648–5652. doi:10.1002/anie.200902029.

The True Structures of the Vannusals, Part 2: Total Synthesis and Revised Structure of Vannusal B**

K. C. Nicolaou*, **Adrian Ortiz**, and **Hongjun Zhang**
Department of Chemistry and The Skaggs Institute for Chemical Biology The Scripps Research Institute 10550 North Torrey Pines Road, La Jolla, CA 92037 (USA) and Department of Chemistry and Biochemistry University of California, San Diego 9500 Gilman Drive, La Jolla, CA 92093 (USA)

Keywords

vannusals A & B; structural revision; total synthesis

In the preceding communication[1] we described our initial attempts to determine the true structures of the vannusals [A (**1**) and B (**2**), originally assigned structures, Figure 1]. Herein, we report the total synthesis of the real vannusal B (i.e. structure **4**, Figure 1) that served not only to render it available for biological investigations, but also to demystify its true molecular architecture and that of its sibling, vannusal A.

Our initial intelligence gathering efforts led us to the conclusion that (a) the stereochemical details of the "bottom" part of the molecule (i.e. rings A and B, C_3, C_{29}, C_6, and C_7) were most likely correct as reported in the originally assigned structures **1** and **2**, and (b) the most likely place for an error was the very "top" part of those structures (i.e. ring E, C_{25} and C_{21}). Since we had already synthesized three of the four C_{25}/C_{21} possible diastereomers of the originally assigned structure of vannusal B (**2**)[2] and found them to be erroneous, we returned to the remaining diastereomer, structure **3** [C_{25}-*epi*-**2**,Figure 1], as a possible candidate for the true structure of vannusal B. By virtue of its *trans* stereochemistry at C_{25}/C_{21}, structure **3** was abandoned earlier on the basis of the large coupling constant observed between H_{21} and H_{25} (J = 8.5 Hz) in the *trans* substituted C_{21}-*epi*-**2** isomer (structure **3**, in ref 1). This led us to the chase of several other diastereomers which, as we have seen in the preceding communication, [1] ended by proving that none of them represented the true structure of vannusal B.

With all the evidence in front of us, we were now forced to reconsider the possibility that the C_{25}-*epi*-**2** structure (i.e. **3**, Figure 1) may accommodate the observed smaller coupling constant for natural vannusal B ($JH_{25,21}$ = 1.6 Hz) by virtue of a special conformation. We, therefore, decided to pursue the synthesis of **3** as the possible coveted structure of vannusal B. The selection of structure **3** as our next favorite target defined compounds **5** and **6** (Figure 1) as the required building blocks for its construction. From these two fragments, only **6** needed to be synthesized, since **5** was already available in enantiopure form from our previous studies.[2] Its synthesis begun with the DIBAL-H reduction of racemic **8** [obtained by reaction of the titanium enolate of diketone (±)-**7** ($TiCl_4$, Et_3N) with acetone][2] which proceeded

[**]We thank Professor Graziano Guella for samples and NMR spectra of vannusals A and B, and for helpful discussions. We thank Drs. D. H. Huang, G. Siuzdak and R. Chadha for NMR spectroscopic, mass spectroscopic and X-ray crystallographic assistance, respectively. Financial support for this work was provided by the NSF (fellowship to A. Ortiz), the Skaggs Institute for Research, and a grant from the National Institutes of Health (USA).

[*]Fax: (+1) (858) 784-2469 kcn@scripps.edu.

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stereoselectively (ca. 6:1 *dr*) from the α-face of the molecule and at both carbonyl sites to afford, upon chromatographic purification, pure triol **9** in 64 % overall yield (Scheme 1). The diastereoselective reduction of (±)-**8** stands in contrast to the $NaBH_4$ reduction of its TES-protected counterpart, which gave the opposite stereochemistry at C_{25}.[2]

Interestingly, triol **9** exhibited a small coupling constant between H_{25} and H_{21} ($JH_{25,21}$ = 1.0 Hz), which was rather surprising given the coupling constants between the same protons of its siblings, **9a** ($JH_{25,21}$ = 10.0 Hz),[1] **9b** ($JH_{25,21}$ = 3.5 Hz),[1] and **9**c ($JH_{25,21}$ < 1.0 Hz)[2] (see Figure 2). Particularly striking was the difference between the two *trans* compounds **9** ($JH_{25,21}$ = 1.0 Hz) and **9a** ($JH_{25,21}$ = 10.0 Hz). An X-ray crystallographic analysis[3] (see ORTEP drawing, Figure 2) of tetraol **9d** (mp 139–141 °C, benzene/MeOH) (obtained from **9** by desilylation with aq. HF as shown in Scheme 1) confirmed the assigned stereochemical relationships within triol **9**. These observations underscored the dangers of relying on the coupling constants to assign stereochemistry around 5-membered rings, and provided somewhat of an endorsement of our choice of target **3** as a candidate for the true structure of vannusal B.

Returning to the main sequence of Scheme 1, installment of SEM groups on all three hydroxyl groups of intermediate **9** required sequential treatment with SEMCl and *i*Pr_2NEt (50 °C, 24 h) first, followed by the use of KHMDS and excess SEMCl to deliver the corresponding tri-SEM derivative **10** (96 % overall yield). The remaining steps to the targeted fragment (±)-**6** followed the previously chartered route[1] and proceeded in high overall yield through intermediates **11**–**13** as summarized in Scheme 1.

The coupling of enantiopure vinyl iodide (−)-**5**[2] with racemic aldehyde (±)-**6** (see Scheme 2) proceeded smoothly through the lithio derivative of **5** (*t*BuLi) to afford, after removal of the TIPS group (TBAF, 25 °C), a mixture of diastereomeric diols **14a** and **14b** (84 % for two steps, ca. 1:1 *dr*), which were chromatographically separated. Based on our previous studies,[4] the undesired diastereomers (such as **14b**) had been routinely utilized for reconnaissance studies regarding late stage transformations, particularly the SmI_2-cyclization and final global deprotection. Consequently, both coupling products **14a** and **14b** were separately converted to cyclization precursors **15a** ad **15b**, respectively, through the same sequence of reactions involving temporary silylation of the primary hydroxyl group (TESCl, imid.), carbonate formation at the secondary position (KHMDS, $ClCO_2Me$), removal of the TES group (HF•py, 89 % yield for **14a**, 96 % yield for **14b**), and oxidation of the liberated primary hydroxyl group [$PhI(OAc)_2$, AZADO (cat.),[5] 96 % yield for **15a**, 97 % yield for **15b**] as summarized in Scheme 2.

First to be advanced from this point was intermediate **15a** possessing our favorite diastereomeric configuration. Much to our disappointment, precursor **15a** with its three SEM groups in place failed to undergo the desired SmI_2-induced ring closure as several of its previous siblings,[1,2] thus prompting us to modify its structure as a means to adjust its reactivity. To this end, **15a** was treated with aq. HF to afford, cleanly, dihydroxy substrate **16** (81 % yield) through selective cleavage of the C_{22} and C_{26} SEM groups (Scheme 2). Pleasantly, substrate **16** underwent the desired SmI_2-induced cyclization to afford polycyclic structure **17** as the major product (67 % yield), possessing, however, the undesired C_{10}/C_{28} stereochemistry as shown in Scheme 3. The obligatory inversion of the stereochemistry at C_{10} and C_{28} of product **17** required a sequence that initially involved selective temporary acetylation at C_{28} (Ac_2O, Et_3N, 4-DMAP, 100 % yield), installation of a SEM group at C_{22} (SEMCl, *i*Pr_2NEt), and deacetylation (DIBAL-H) to furnish diol **19**, in 83 % overall yield. Selective xanthate formation at C_{28} followed by *syn*-elimination (NaH, CS_2, MeI, 79 % yield; then μ-waves; 185 °C, 88 % yield) to afford, after SEM protection of the C_{26}-OH group, conjugate diene **20** (78 % yield). The latter compound was converted to the desired C_{10}/C_{28}

diastereomer **21** through the previously developed sequence involving hydroboration/oxidation ($ThexBH_2$; BH_3; H_2O_2, 71% yield) and phenylselenenylation/*syn*-elimination (*o*$NO_2C_6H_4$ SeCN, *n*Bu_3P; H_2O_2, 86 % yield). Intermediate **21** was then transformed to diol **22** through sequential silylation (KHMDS, TESCl, 93 % yield) and cleavage of the BOM groups (LiDBB, 85 % yield). The final three steps to structure **3** involving sequential oxidation of the primary hydroxyl group within **22** [$PhI(OAc)_2$, TEMPO, 88 % yield], acetylation of the secondary hydroxyl group (Ac_2O, Et_3N, 4-DMAP, 100 % yield), and global desilylation (aq. HF, 90 % yield) proceeded smoothly to afford vannusal B structure **3**, but not before the completion of the synthesis of vannusal B structure **4** (vide infra), which we will describe next because of its special significance.

Scheme 4 summarizes the total synthesis of vannusal B structure **4**. As it turned out, this synthesis was shorter and more efficient than that of vannusal B structure **3**. Thus, remarkably and in stark contrast to the attempted cyclization of its diastereomeric counterpart (**15a**), the SmI_2-mediated ring closure of precursor **15b** proceeded smoothly and in high yield (82 %) to afford polycyclic compound **24** as a single diastereomer. Furthermore and much to our delight, the two newly formed stereogenic centers C_{10} and C_{28} possessed the correct stereochemistry relative to the adjacent quaternary centers, needing no configurational adjustment as previously required. Placement of a TES group on the C_{28} hydroxyl group of **24** (KHMDS, TESCl), followed by removal of the two BOM groups (LiDBB), led to diol **25**, in 78 % overall yield for the two steps. Selective oxidation of the primary alcohol within the latter compound was best achieved through the use of $PhI(OAc)_2$ in the presence of 1-Me-AZADO[5] as a catalyst, affording aldehyde **26** whose remaining hydroxyl group was acetylated (Ac_2O, 4-DMAP) to give protected vannusal B structure **26** (87% yield for the two steps). Finally, the coveted structure **4** was generated from **26**, in 85% yield, by exposure to aq. HF at ambient temperature.

The 500 MHz ^1H NMR spectrum of synthetic vannusal B structure **4** appeared excitingly close to the 600 MHz ^1H NMR spectrum of natural vannusal B that we had in our possession,[6] a fact that piqued our enthusiasm for the soon to be completed structure **3** (see Scheme 3), which still commanded our main attention. Our arrival at vannusal B structure **3** (Scheme 3), however, was met with grief, for the 600 MHz ^1H NMR spectrum of this compound did not match that (also 600 MHz) of the natural product. Thankfully, this time our disappointment was short lived, for upon obtaining a 600 MHz ^1H NMR spectrum of synthetic structure **4** (Scheme 4), to which we immediately returned, we realized that it was identical in every detail to that (600 MHz) of natural vannusal B! Indeed, structure **4** represents the true structure, including absolute configuration, of vannusal B as proven by comparison of its ^1H and ^{13}C NMR and CD spectra with those of the natural product. Furthermore, the ^1H and ^{13}C NMR spectral data of the $NaBH_4$ reduction product of synthetic vannusal B (**27**,Scheme 4) also matched those of its counterpart obtained from natural vannusals A and B,[6,7] providing further support of structure **4** as the true structure of vannsual B. The structure of crystalline synthetic vannusal B (mp >200 °C decomposition, EtOAc/THF) was ultimately confirmed by X-ray crystallographic analysis[8] (see ORTEP drawing, Figure 3). The structural differences between the originally assigned and revised structures of vannusal B are located mainly in the "right" domain of the molecule (C_{10}, C_{28}, C_{13}, C_{14}, C_{26}, C_{17}, C_{18} and C_{21} stereocenters inverted), a circumstance that apparently arose from the difficulty in relating the C_7 and C_{10} stereocenters in the original structural studies. This challenge could only be solved either by X-ray crystallographic analysis, or chemical synthesis. In the end it was done by both, the latter preceding the former, demonstrating the facilitating nature of total synthesis in structural elucidation even in this modern era.

The described chemistry underscores once again the indispensable roles of total synthesis in the structural elucidation of scarce natural products and in rendering them in sufficient quantities for further investigations in those cases where their scarcity stymie such studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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[4].

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[7].

[8]. CCDC-726954 contains the supplementary crystallographic data for vannusal B (**4**) and is available from The Cambridge Crystallographic Data Centre free of charge viawww.ccdc.cam.ac.uk/data_request/cif

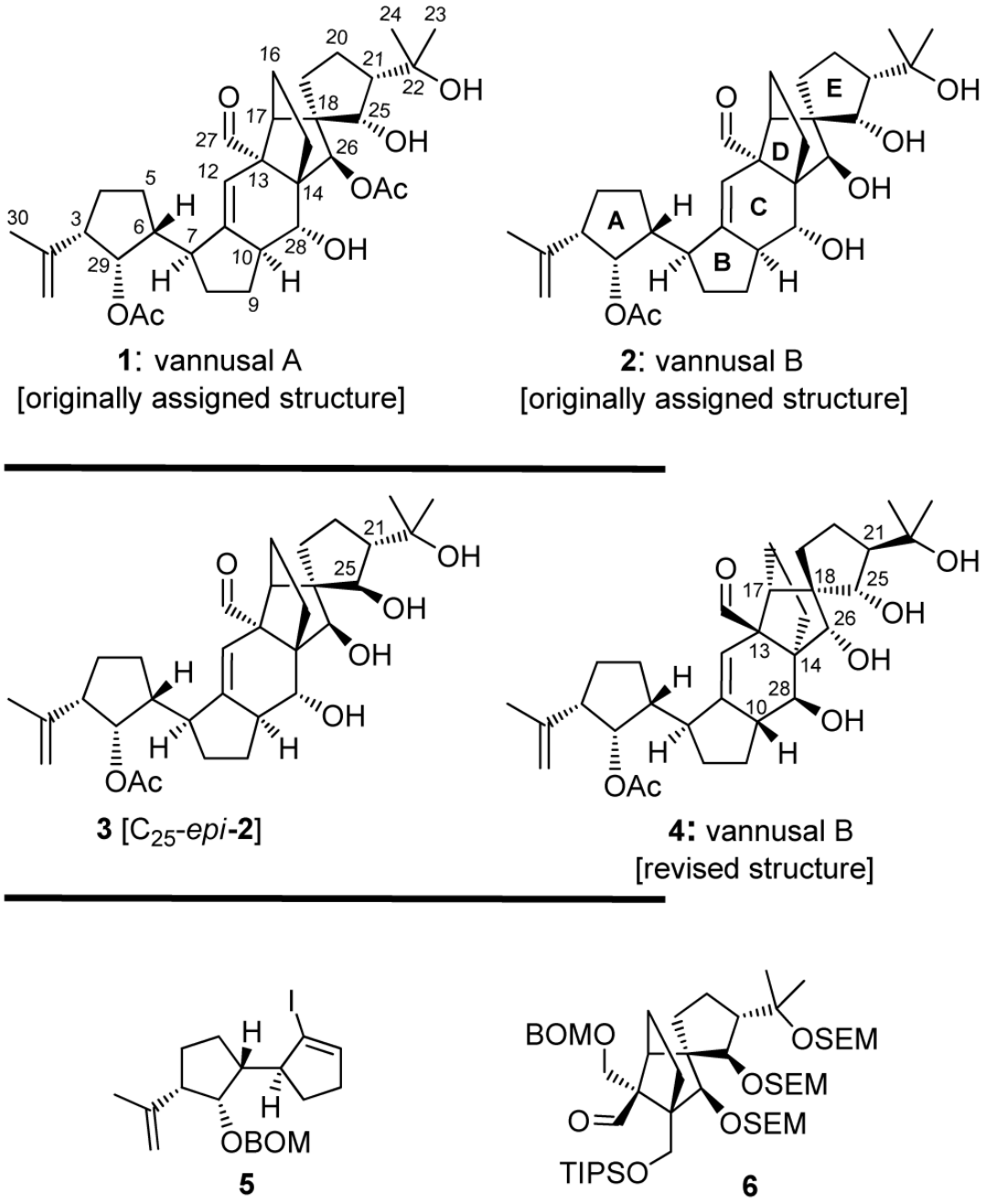


Figure 1.
Originally assigned structures of vannusals A (**1**) and B (**2**), final targeted stereoisomer **3** [C_{10}-*epi*-**2**], and revised structure **4**. BOM = benzyloxymethyl; SEM = trimethylsilylethoxymethyl; TIPS = triisopropylsilyl.

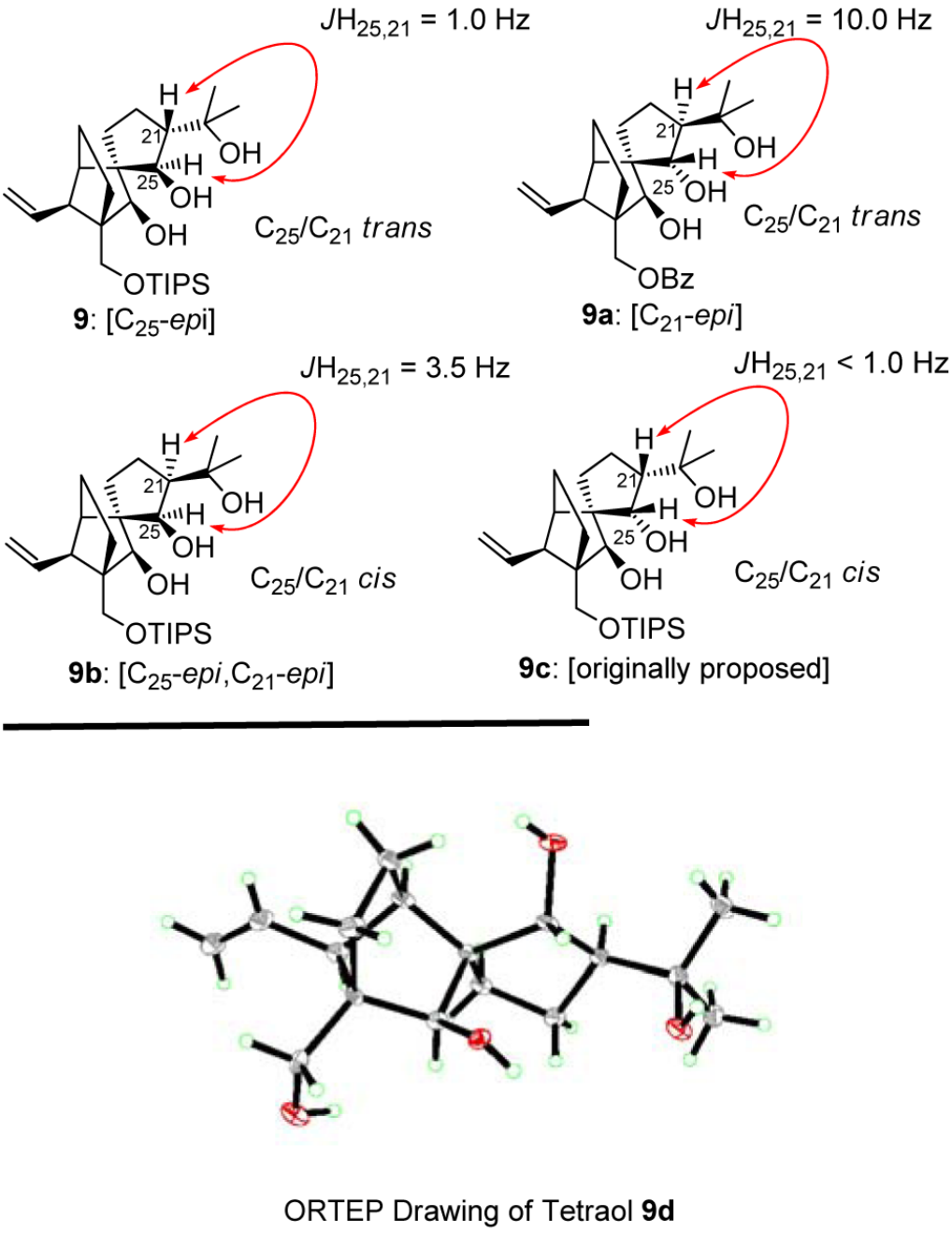
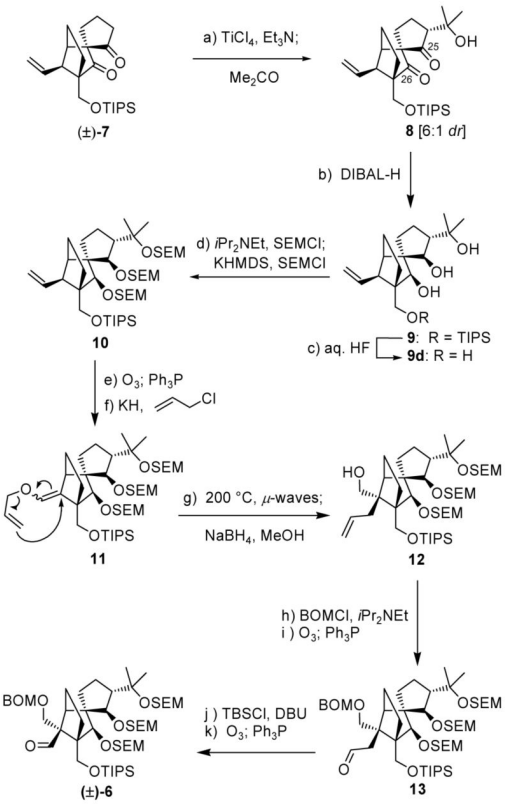


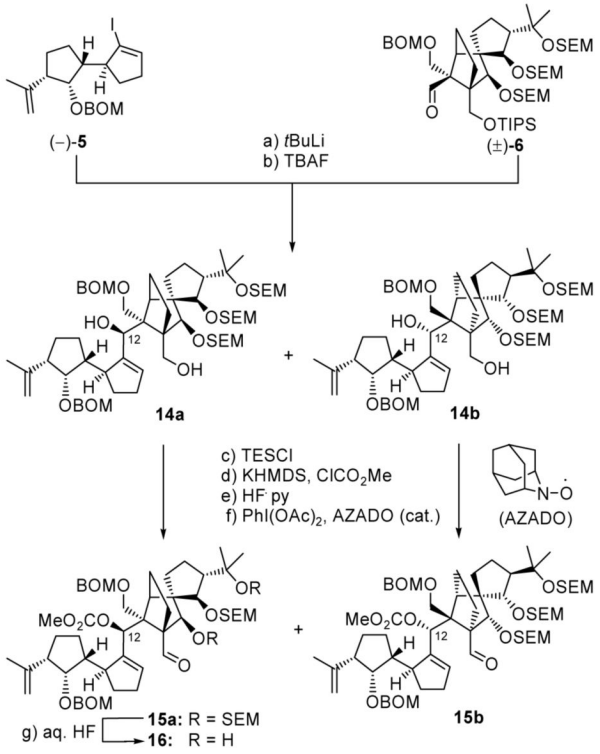
Figure 2.
Key ^{1}H NMR coupling constants for tricyclic intermediates **9** ($JH_{25,21}$ = 1.0 Hz), **9a** ($JH_{25,21}$ = 10.0 Hz), **9b** ($JH_{25,21}$ = 3.5 Hz), and **9c** ($JH_{25,21}$ < 1.0 Hz) (top), and X-ray derived ORTEP drawing of tetraol **9d** (bottom).

Figure 3.
X-ray derived ORTEP drawing of vannusal B (**4**) (Thermal ellipsoids are shown at 30 % probability).



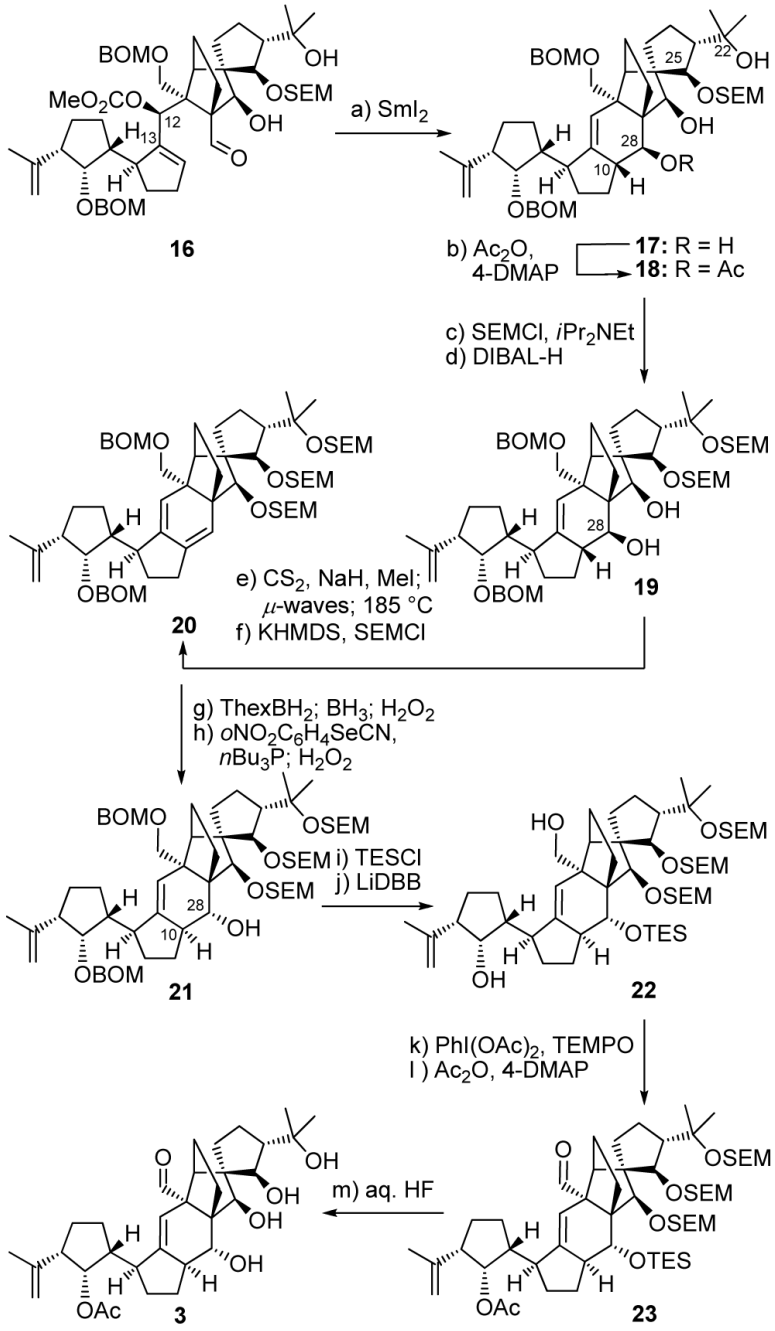
Scheme 1.

Construction of aldehyde (±)-**6**. Reagents and conditions: (a) $TiCl_4$ (1.3 equiv), Et_3N (3.0 equiv), acetone (10 equiv), CH_2Cl_2, −92 °C, 8 h; (b) DIBAL-H (5.0 equiv), PhMe, −78→0 °C, 30 min, 64 % for two steps; (c) aq. HF:THF (1:4), 25 °C, 18 h, 83 %; (d) *i*Pr_2NEt (20 equiv), SEMCl (6.0 equiv), *n*Bu_4NI (1.0 equiv), 50 °C, 24 h; KHMDS (3.0 equiv), SEMCl (5.0 equiv), Et_3N (10 equiv), THF, −78→25 °C, 1 h, 96 % for the two steps; (e) O_3, py (1.0 equiv), CH_2Cl_2:MeOH (1:1), −78 °C; then Ph_3P (5.0 equiv), −78→25 °C, 1 h, 97 %; (f) KH (10 equiv), allyl chloride (30 equiv), HMPA (10 equiv), DME, −10→25 °C, 8 h, 95 %; (g) *i*Pr_2NEt (1.0 equiv), 1,2-dichlorobenzene, 200 °C (*μ*-waves), 20 min; then $NaBH_4$ (10 equiv), MeOH, 1 h, 25 °C, 88 % for two steps; (h) BOMCl (10 equiv), *i*Pr_2NEt (30 equiv), *n*Bu_4NI (1.0 equiv), CH_2Cl_2, 50 °C 12 h; (i) O_3, py (1.0 equiv), CH_2Cl_2:MeOH (1:1), −78 °C; then Ph_3P (5.0 equiv), −78→25 °C, 1 h, 81 % for two steps; (j) TBSCl (10 equiv), DBU (20 equiv), CH_2Cl_2, 25 °C, 12 h; (k) O_3, py (1.0 equiv), CH_2Cl_2:MeOH (1:1), −78 °C; then Ph_3P (5.0 equiv), −78→25 °C, 1 h, 80 % for two steps. HMPA = hexamethylphosphoramide, DBU = 1,8-diazoicyclo[5.4.0] undec-7-ene.



Scheme 2.

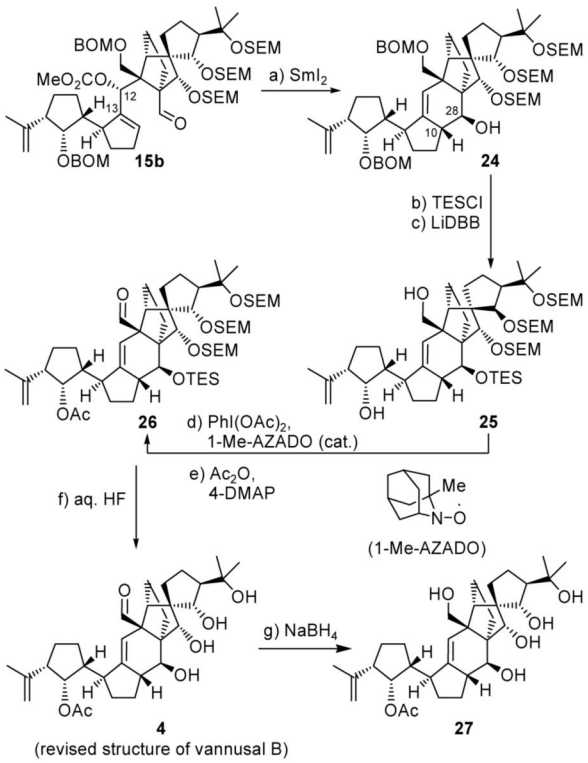
Coupling of fragments (−)-**5** and (±)-**6**. Reagents and conditions: (a) (−)-**5** (1.3 equiv), *t*BuLi (2.6 equiv), THF, −78→−40 °C, 40 min; then (±)-**6** (1.0 equiv), −40→0 °C, 20 min; (b) TBAF (1.0 M in THF, 2.0 equiv), THF, 25 °C, 8 h, 84 % (ca. 1:1 *dr*) for the two steps, **14a** and **14b** chromatographically separated; c) TESCl (2.0 equiv), imid (10 equiv), CH_2Cl_2, 25 °C, 30 min; (d) KHMDS (10 equiv), $ClCO_2Me$ (20 equiv), Et_3N (20 equiv), THF, −78→25 °C, 30 min; (e) HF•py / py (1:4), 0→25 °C, 12 h, 89 % for sequence **14a**→**15a**, 96 % for sequence **14b**→**15b** (for three steps); (f) $PhI(OAc)_2$ (2.0 equiv), AZADO (0.1 equiv), CH_2Cl_2, 25 °C, 24 h, (96 % for **15a**, 97 % for **15b**); (g) aq. HF:THF (1:4), 25 °C, 1.5 h, 81 %.



Scheme 3.

Synthesis of vannusal B structure **3**. Reagents and conditions: (a) SmI_2 (0.1 M in THF, 10 equiv), HMPA (30 equiv), THF, −20→25 °C, 20 min, 67 %; (b) Ac_2O (20 equiv), Et_3N (20 equiv), 4-DMAP (0.2 equiv), CH_2Cl_2, 25 °C, 30 min, 100 %; (c) SEMCl (10 equiv), $i Pr_2NEt$ (30 equiv), CH_2Cl_2, 50 °C, 18 h; (d) DIBAL-H (5.0 equiv), CH_2Cl_2, −78 °C, 30 min, 83 % for two steps; (e) NaH (10 equiv), CS_2 (3.0 equiv), THF, 0→25 °C, 30 min; then CH_3I (6.0 equiv), 0→25 °C, 1 h, 79 %; then 185 °C (*μ*–waves), 1,2-dichlorobenzene, 15 min, 88 %; (f) KHMDS (4.0 equiv), SEMCl (4.0 equiv), Et_3N (8.0 equiv), THF, −50→25 °C, 20 min, 78 %; (g) $ThexBH_2$ (5.0 equiv), THF, −10→25 °C, 30 min; then BH_3•THF (15 equiv), 25 °C, 1 h; then 30 % H_2O_2/3 N NaOH (1:1 *dr*), 25→45 °C, 30 min; 71 % (1:1.3 mix); (h) $oNO_2C_6H_4SeCN$

(3.0 equiv), *n*Bu_3P (9.0 equiv), py (12.0 equiv), THF, 25 °C, 10 min; then 30 % H_2O_2, 25→45 °C, 30 min, 86 %; (i) KHMDS (6.0 equiv), TESCl (4.0 equiv), Et_3N (8.0 equiv), THF, −50→25 °C, 20 min, 93 %; (j) LiDBB (excess), THF, −78→−50 °C, 30 min, 85 %; (k) $PhI(OAc)_2$ (4.0 equiv), TEMPO (2.0 equiv), CH_2Cl_2, 25 °C, 15 h, 88 %; (l) Ac_2O (30 equiv), Et_3N (60 equiv), 4–DMAP (2.0 equiv), CH_2Cl_2, 25 °C, 24 h, 100 %; (m) aq. HF:THF (1:3), 25 °C, 6 h, 90 %. KHMDS = potassium hexamethyldisilyazide, TEMPO = 2,2,6,6-teramethyl-1-piperidinyloxy free radical, Thexyl = thexylborane, LiDBB = Lithium di-*tert*-butylbiphenyl.



Scheme 4.

Completion of the revised structure of vannusal B (**4**). Reagents and conditions: (a) SmI_2 (0.1 M in THF, 10 equiv), HMPA (30 equiv), THF, −20→25 °C, 30 min, 82 %; (b) KHMDS (5.0 equiv), TESCl (10 equiv), Et_3N (10 equiv), THF, −78→25 °C, 20 min, 94 %; (c) LiDBB (excess), THF, −78→−50°C, 30 min, 83 %; (d) $PhI(OAc)_2$ (2.0 equiv), 1-Me-AZADO (0.2 equiv), CH_2Cl_2, 25 °C, 18 h; (e) Ac_2O (10 equiv), Et_3N (20 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 18 h, 87 % for two steps; (f) aq. HF:THF (1:4→1:3), 25 °C, 3 h, 85 %; (g) $NaBH_4$ (20 equiv), MeOH, 20 min, 90 %.