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

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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** in 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 "southwestern" 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 of the "northeastern" region of those structures (i.e. ring E, C_{25} and C_{21}). As we had already synthesized three of the four possible C_{25}/C_{21} 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* configuration 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 observation led us to chase 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 favored target defined compounds **5** and **6** (Figure 1) as the required building blocks for its construction. Of these two fragments, only **6** needed to be synthesized, since **5** was already available in enantiopure form from our previous studies.[2] Its synthesis began with reduction of racemic **8** [obtained by reaction of the titanium enolate of diketone (±)-**7** ($TiCl_4$, Et_3N) with acetone (ca. 6:1 d.r.)][2] using DIBAL-H, which proceeded stereoselectively from the α face of the molecule and at both carbonyl sites to afford, upon purification by chromatography, pure triol **9** in 64% yield over two steps (Scheme 1). The diastereoselective reduction of (±)-**8** with $NaBH_4$ stands in contrast to the reduction of its TES-protected counterpart, which gave the opposite configuration 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** ($JH_{25,21} =$

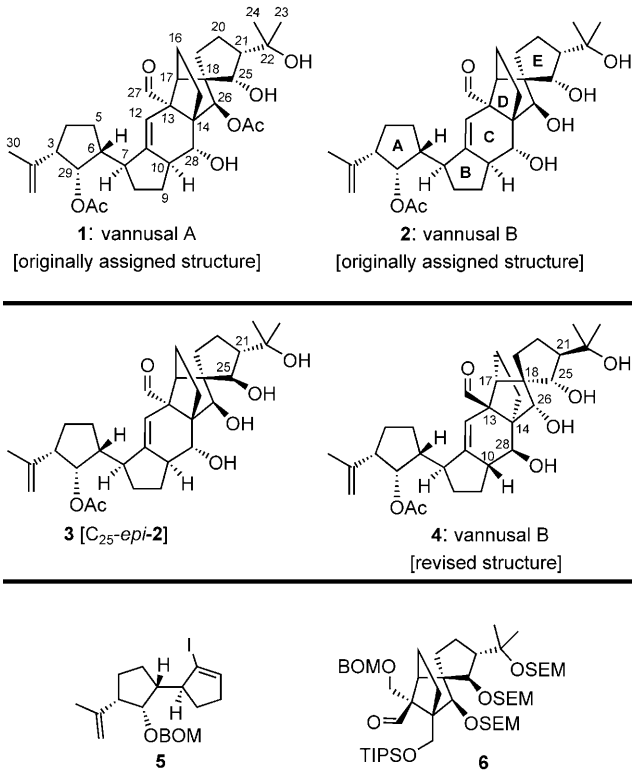

Figure 1. Originally assigned structures of vannusals A (**1**) and B (**2**), final targeted stereoisomer **3** [C_{25}-*epi*-**2**], and revised structure **4**. BOM = benzyloxymethyl, SEM = trimethylsilylethoxymethyl, TIPS = triisopropylsilyl.

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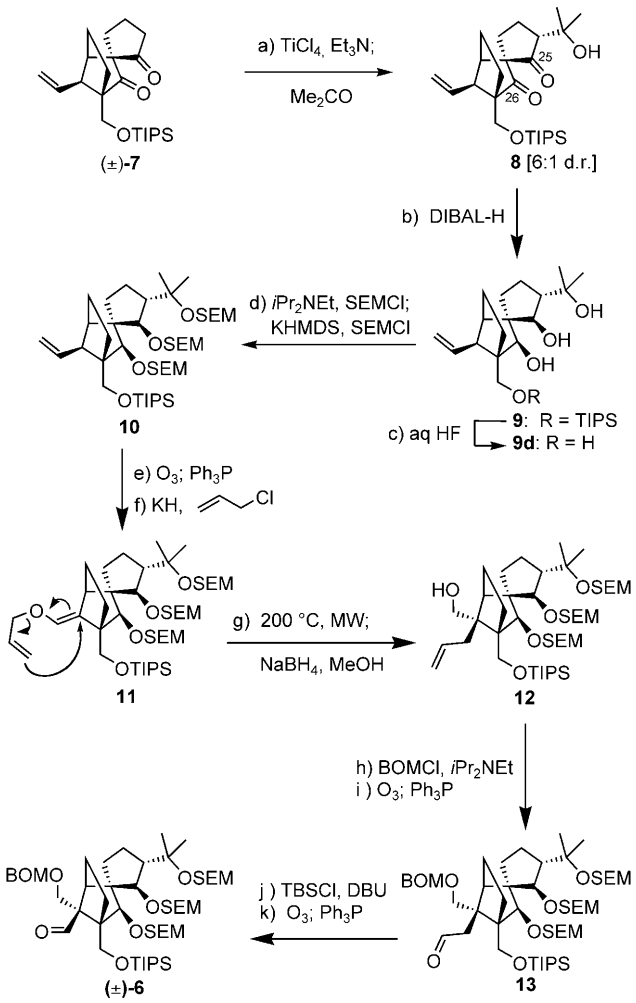


Scheme 1. Construction of aldehyde (±)-**6**. Reagents and conditions: a) $TiCl_4$ (1.3 equiv), Et_3N (3.0 equiv), acetone (10 equiv), CH_2Cl_2, −92 °C, 8 h; b) DIBAL-H (5.0 equiv), toluene, −78→0 °C, 30 min, 64% over two steps; c) aq HF/THF (1:4), 25 °C, 18 h, 83%; d) iPr_2NEt (20 equiv), SEMCl (6.0 equiv), nBu_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% over 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) iPr_2NEt (1.0 equiv), 1,2-dichlorobenzene, 200 °C (MW), 20 min; then $NaBH_4$ (10 equiv), MeOH, 1 h, 25 °C, 88% over two steps; h) BOMCl (10 equiv), iPr_2NEt (30 equiv), nBu_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% over 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% over two steps. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DIBAL-H = diisobutylaluminum hydride, DME = 1,2-dimethoxyethane, HMDS = hexamethyldisilazane, HMPA = hexamethylphosphoramide, py = pyridine, TBS = *tert*-butyldimethylsilyl.

3.5 Hz),[1] and **9c** ($JH_{25,21} < 1.0$ 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** (obtained from **9** by desilylation with aqueous HF as shown in Scheme 1; m.p. 139–141 °C, benzene/MeOH) confirmed the assigned stereochemical relationships

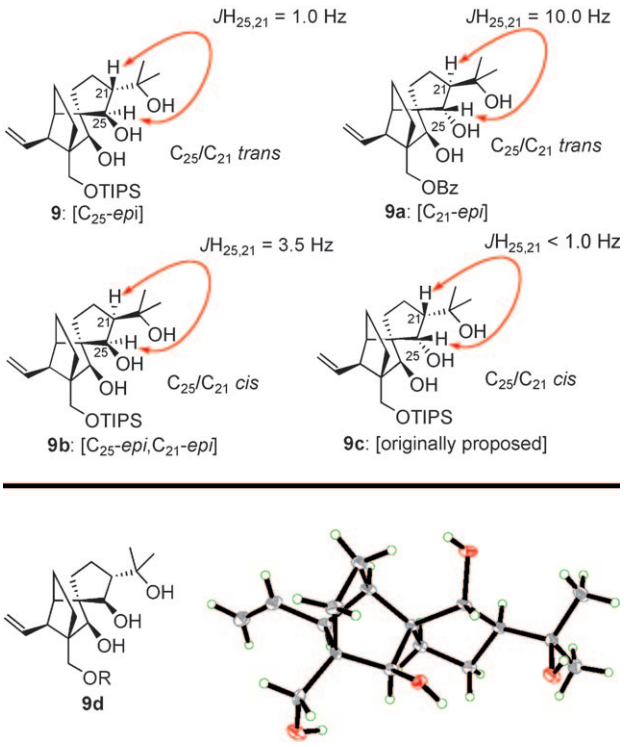
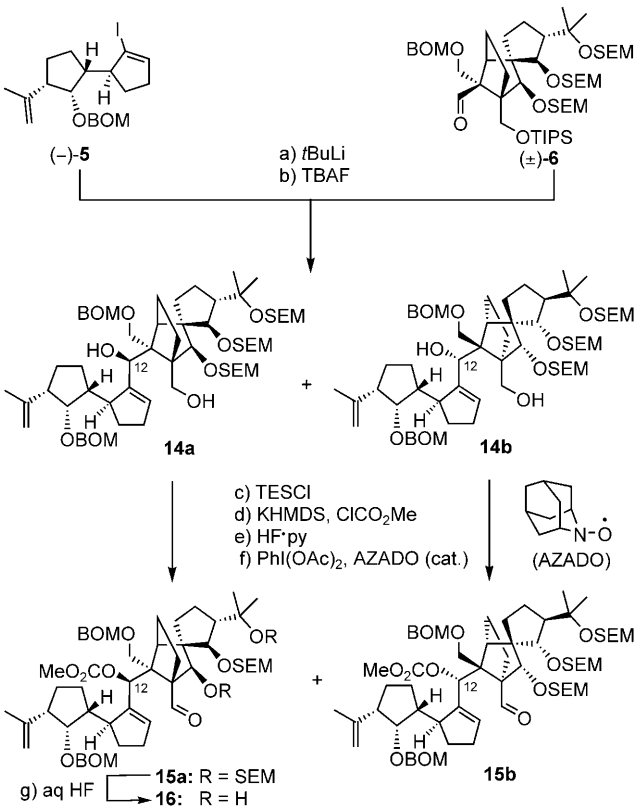


Figure 2. Key ^1H NMR coupling constants for tricyclic intermediates **9** ($JH_{25,21} = 1.0$ Hz), **9a** ($JH_{25,21} = 10.0$ Hz), **9b** ($JH_{25,21} = 3.5$ Hz), and **9c** ($JH_{25,21} < 1.0$ Hz) (top), and X-ray crystal structure of tetraol **9d** (bottom; ORTEP: thermal ellipsoids are shown at 30% probabliity). Bz = benzoyl.

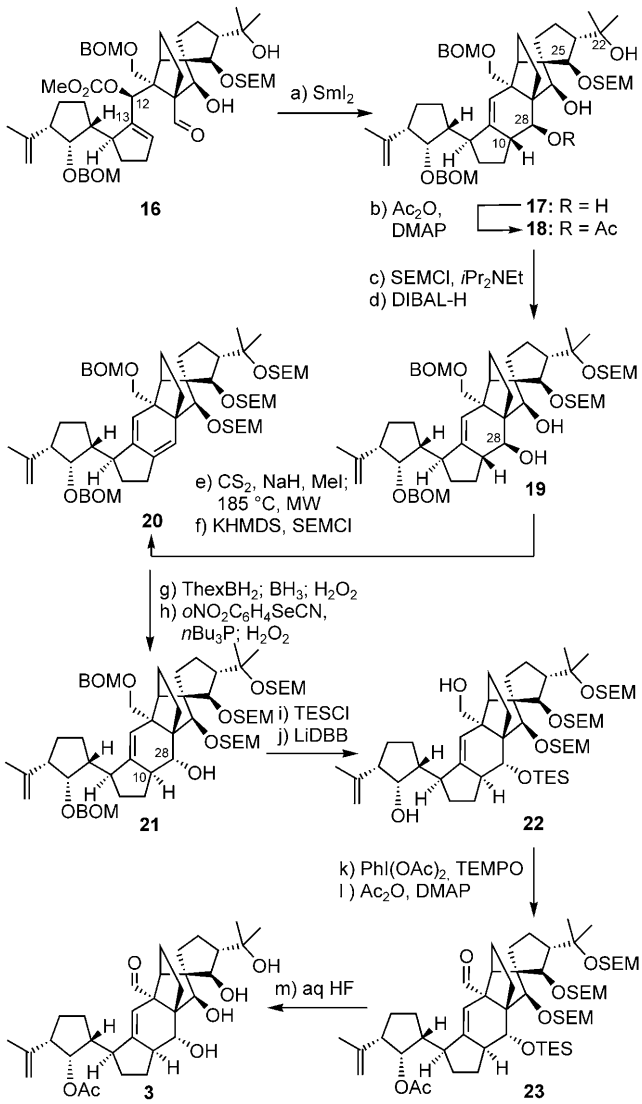
within triol **9**. These observations underscored the dangers of relying on the coupling constants to assign configurations around five-membered rings, and provided somewhat of an endorsement of our choice of target **3** as a candidate for the true structure of vannusal B.

Returning to the main sequence of Scheme 1, installment of SEM groups on all three hydroxy groups of intermediate **9** required sequential treatment with SEMCl and iPr_2NEt (50 °C, 24 h) first, and subsequent 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** (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% over 2 steps, ca. 1:1 d.r.), which were separated by chromatography. 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 into cyclization precursors **15a** and **15b**, respectively, through the same sequence of reactions involving temporary silylation of the primary hydroxy group (TESCl, imid), carbonate



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 d.r.) over two steps, **14a** and **14b** separated by chromatography; 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** (over 3 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%. imid = imidazole, TBAF = tetra-*n*-butylammonium fluoride, TES = triethylsilyl, THF = tetrahydrofuran.



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), DMAP (0.2 equiv), CH_2Cl_2, 25 °C, 30 min, quant.; c) SEMCl (10 equiv), iPr_2NEt (30 equiv), CH_2Cl_2, 50 °C, 18 h; d) DIBAL-H (5.0 equiv), CH_2Cl_2, −78 °C, 30 min, 83% over 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 (MW), 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 d.r.), 25→45 °C, 30 min; 71% (1:1.3 d.r.); h) $oNO_2C_6H_4SeCN$ (3.0 equiv), nBu_3P (9.0 equiv), py (12 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), DMAP (2.0 equiv), CH_2Cl_2, 25 °C, 24 h, quant.; m) aq HF/THF (1:3), 25 °C, 6 h, 90%. DMAP = 4-dimethylaminopyridine, LiDBB = lithium di-*tert*-butylbiphenyl, TEMPO = 2,2,6,6-teramethyl-1-piperidinyloxy (free radical), Thexy = thexyl.

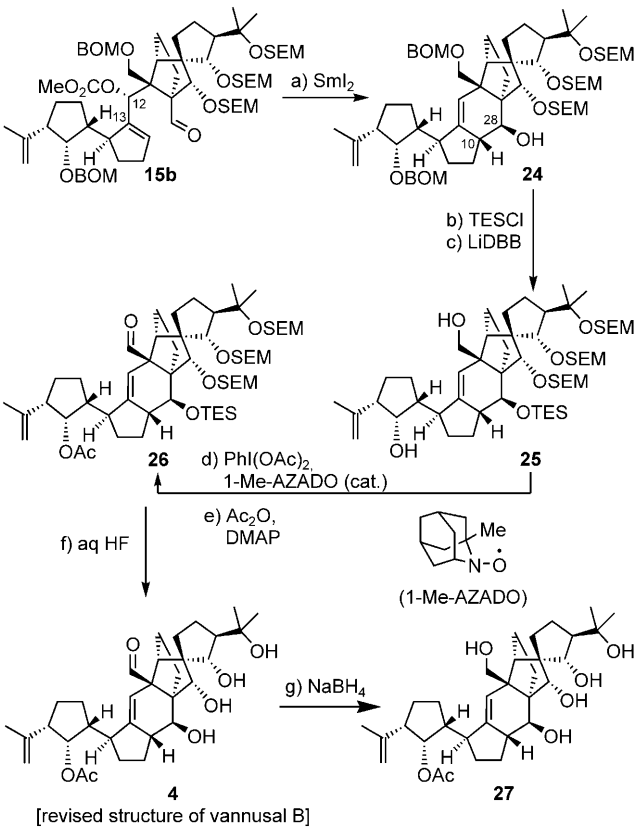
formation at the secondary position (KHMDS, $ClCO_2Me$), removal of the TES group (HF·py; 89% yield for **14a**, 96% yield for **14b**), and oxidation of the liberated primary hydroxy group [$PhI(OAc)_2$, AZADO (cat.),[5] 96% yield for **15a**, 97% yield for **15b**], as summarized in Scheme 2.

First to be advanced from this point was intermediate **15a**, which possessed our favored 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 aqueous HF to afford, cleanly, dihydroxy substrate **16** (81% yield) through selective cleavage of the SEM groups at C_{22} and C_{26} (Scheme 2). Pleasantly, substrate **16** underwent the desired SmI_2-induced cyclization to afford polycyclic structure **17** as the major product (67% yield), which possessed, however, the undesired configuration at C_{10} and C_{28} as shown in Scheme 3. The obligatory inversion of the configuration 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, DMAP, quantitative yield), installation of a SEM group at C_{22}

(SEMCl, iPr$_2$NEt), and deacetylation (DIBAL-H) to furnish diol **19**, in 83% yield over two steps. Selective formation of a xanthate at C_{28} and subsequent *syn* elimination [NaH, CS_2, MeI, 79% yield; then microwave (MW) heating, 185°C, 88% yield] afforded, after protection of the hydroxy group at C_{26} with an SEM group, conjugate diene **20** (78% yield). The latter compound was converted into 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 (oNO$_2$C$_6$H$_4$ SeCN, nBu$_3$P; H_2O_2, 86% yield). Intermediate **21** was then transformed into 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**, which involved sequential oxidation of the primary hydroxy group within **22** (PhI(OAc)$_2$, TEMPO, 88% yield), acetylation of the secondary hydroxy group (Ac$_2$O, Et$_3$N, DMAP, quantitative 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** (see below), 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 efficiently (82% yield) to afford polycyclic compound **24** as a single diastereomer. Furthermore and much to our delight, the two newly formed stereogenic centers at C_{10} and C_{28} possessed the correct configuration relative to the adjacent quaternary centers, thus needing no configurational adjustment as previously required. Placement of a TES group on the hydroxy group at C_{28} of **24** (KHMDS, TESCl), and subsequent removal of the two BOM groups (LiDBB), led to diol **25** in 78% yield over 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 to afford aldehyde **26**, whose remaining hydroxy group was acetylated (Ac$_2$O, DMAP) to give protected vannusal B structure **26** (87% yield over 2 steps). Finally, the coveted structure **4** was generated from **26**, in 85% yield, by exposure to aqueous HF at ambient temperature.

The 500 MHz ^{1}H NMR spectrum of synthetic vannusal B structure **4** appeared excitingly close to the 600 MHz ^{1}H 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 because the 600 MHz ^{1}H NMR spectrum of this compound did not match that (also 600 MHz) of the natural product. Thankfully, our disappointment was short lived this time, for upon obtaining a 600 MHz ^{1}H 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



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$_3$N (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$_2$Cl$_2$, 25°C, 18 h; e) Ac$_2$O (10 equiv), Et$_3$N (20 equiv), DMAP (1.0 equiv), CH$_2$Cl$_2$, 25°C, 18 h, 87% over two steps; f) aq HF/THF (1:4→1:3), 25°C, 3 h, 85%; g) NaBH$_4$ (20 equiv), MeOH, 20 min, 90%.

structure, including absolute configuration, of vannusal B as proven by comparison of its ^{1}H and ^{13}C NMR and CD spectra with those of the natural product. Furthermore, the ^{1}H and ^{13}C NMR spectroscopic 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] thus providing further support of structure **4** as the true structure of vannsual B. The structure of crystalline synthetic vannusal B (m.p. > 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 "eastern" domain of the molecule (C_{10}, C_{28}, C_{13}, C_{14}, C_{26}, C_{17}, C_{18}, and C_{21} stereocenters were inverted), a circumstance that apparently arose from the difficulty in relating the stereocenters at C_7 and C_{10} 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, thereby demonstrating the facilitating nature of total synthesis in structural elucidation even in this modern era.

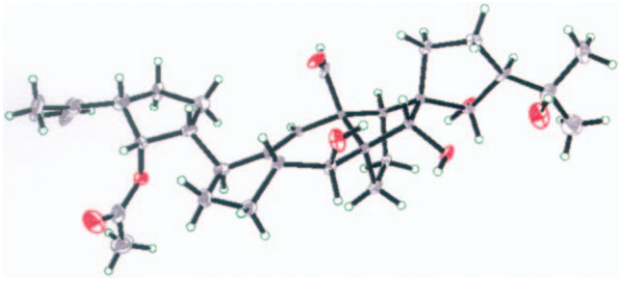


Figure 3. X-ray crystal structure of vannusal B (**4**; thermal ellipsoids are shown at 30% probability).

The chemistry described here 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.

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[1] K. C. Nicolaou, H. Zhang, A. Ortiz, *Angew. Chem.* **2009**; *121*, 5752; *Angew. Chem. Int. Ed.* **2009**, *48*, 5642, see the preceding communication in this issue.

[2] K. C. Nicolaou, H. Zhang, A. Ortiz, P. Dagneau, *Angew. Chem.* **2008**, *120*, 8733 – 8738; *Angew. Chem. Int. Ed.* **2008**, *47*, 8605 – 8610.

[3] CCDC 726955 (**9d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[4] Details of these studies will be reported in the full account of this work.

[5] M. Shibuya, M. Tomizawa, I. Suzuki, Y. Iwabuchi, *J. Am. Chem. Soc.* **2006**, *128*, 8412 – 8413.

[6] G. Guella, F. Dini, F. Pietra, *Angew. Chem.* **1999**, *111*, 1217 – 1220; *Angew. Chem. Int. Ed.* **1999**, *38*, 1134 – 1136.

[7] We thank Prof. Graziano Guella for samples of vannusals A and B, ^{1}H and ^{13}C NMR spectra of vannusals A and B as well as their reduction derivative **27**.

[8] CCDC 726954 (**4**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

