Natural Products

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Total Synthesis of the Originally Assigned Structure of Vannusal B**

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Vannusals A (**1a**, Figure 1) and B (**1b**) are two marine natural products notable for their unusual molecular architectures. Isolated from the tropical interstitial ciliate *Euplotes vannus* strains Si121 and BUN3, these intriguing molecules include in their C_{30} molecular framework seven rings and thirteen stereogenic centers, three of which are quaternary. Their structures have been assigned on the basis of mass spectrometric and NMR spectroscopic data and chemical transformations.[1,2] Herein we report the total synthesis of structure **1b** that proved that it does not represent the true structure of vannusal B.

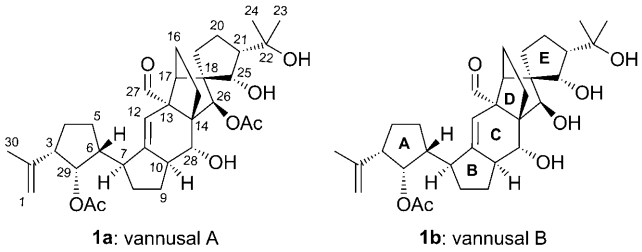

Figure 1. Originally assigned structures of vannusals A (**1a**) and B (**1b**).

Our retrosynthetic analysis of the vannusal molecule dissected it as shown in Figure 2, revealing vinyl iodide **2** and aldehyde **3** as the key building blocks required for the projected total synthesis. The devised strategy anticipated their fusion through two carbon–carbon bond-forming reactions, namely lithiation of **2** followed by addition of **3** to join them, and a samarium-induced ring closure of a subsequent intermediate to forge the final ring of the target molecule.

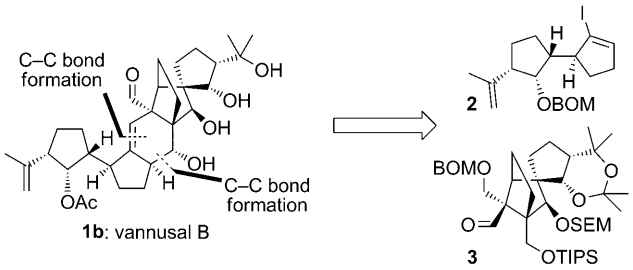

Figure 2. Retrosynthetic analysis of vannusal B (**1b**). BOM = benzyloxymethyl, SEM = trimethylsilylethoxymethyl, TIPS = triisopropylsilyl.

Scheme 1 summarizes the construction of vinyl iodide **2** from the commercially available *meso* diol **4**. Thus, dehydration of **4** through the action of $POCl_3$ (py, 90 °C) furnished conjugated diene **5** (97% yield),[3] which was regio- and stereoselectively converted into the new *meso* diol **6** by a hydroboration–oxidation process ($CyBH_2$; H_2O_2, NaOH, 51% yield). The latter compound was then desymmetrized through the enantioselective hydrolytic action of Lipase Amano PS[4] on its bis-acetate (prepared in quantitative yield by reaction of **6** with Ac_2O in the presence of 4-DMAP), leading to the monoacetate **7** in 100% yield and 99% *ee* (determined by Mosher ester analysis). Silylation of **7** (TBDPSCl, imid, 93% yield) followed by acetate cleavage (DIBAL-H, 98% yield) and treatment of the resulting alcohol with Martin's sulfurane (Et_3N, CH_2Cl_2, 91% yield) afforded enantiomerically pure cyclopentene derivative **8**. The planned stereoselective epoxidation of **8** was achieved through a two-step procedure that involved first iodohydrin formation (NIS, H_2O), and then ring closure (K_2CO_3, MeOH) to give β-epoxide **9** in 91% overall yield. This epoxide was then regio- and stereoselectively opened with 2-lithiopropene (generated from the corresponding bromide and *t*BuLi) in the presence of $BF_3{\cdot}Et_2O$ to afford hydroxy compound **10** (83% yield), whose stereochemistry was inverted through application of a Mitsunobu ($pNO_2C_6H_4CO_2H$, Ph_3P, DEAD)[5]/ester cleavage (DIBAL-H) protocol, leading to the desired hydroxy compound **11** in 90% overall yield. With the proper stereochemistry now installed on **11**, a BOM group was placed on the free hydroxy group (BOMCl, iPr_2NEt) and the TBDPS group was removed (TBAF, 97% overall yield) to furnish compound **12**. The newly generated hydroxy group within **12** was then oxidized [NMO, TPAP (cat.), 96% yield], and the resulting ketone was converted into its tris-hydrazone **13** ($TrisNHNH_2$, 80% yield). Finally, the targeted vinyl iodide **2** emerged in 90% yield through a Shapiro reaction[6] of hydrazone **13** (*n*BuLi, I_2). The relative and absolute stereochemistry of this series of compounds was confirmed by X-ray crystallographic analysis (see ORTEP drawing, Figure 3)[7] of

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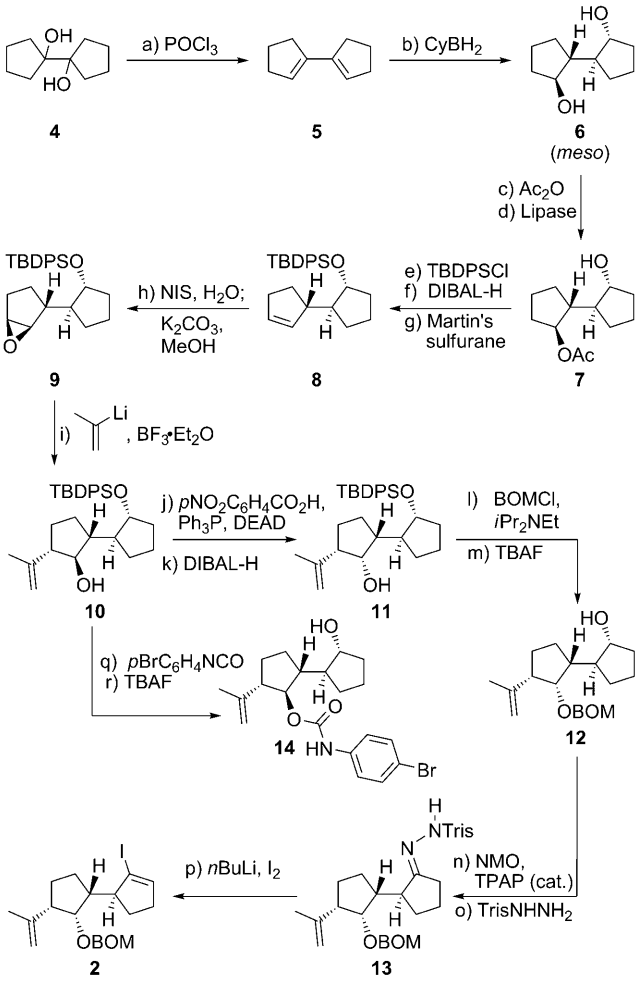


Scheme 1. Enantioselective construction of vinyl iodide **2**. Reagents and conditions: a) $POCl_3$ (2.2 equiv), py, 90 °C, 2 h, 97%; b) BH_3·THF (2.5 equiv), cyclohexene (2.5 equiv), −40→0 °C, 2 h; then **5**, −40→25 °C, 12 h; then 50 °C, 30 min; then 30% H_2O_2/3 N NaOH (2:1 v/v), −50→50 °C, 12 h, 51%; c) Ac_2O (3.0 equiv), 4-DMAP (0.02 equiv), py, 0 °C, 8 h, 100%; d) Lipase Amano PS (100 wt%), acetone/phosphate buffer (pH 7) (2:1), 25 °C, 48 h, 100%, 99% *ee*; e) TBDPSCl (1.2 equiv), imid (3.0 equiv), CH_2Cl_2, 25 °C, 12 h, 93%; f) DIBAL-H (1.0 M in hexanes, 2.5 equiv), CH_2Cl_2, −78 °C, 30 min, 98%; g) Martin's sulfurane (1.3 equiv), Et_3N (3.0 equiv), CH_2Cl_2, 25 °C, 12 h, 91%; h) NIS (1.5 equiv), THF/H_2O (4:1), 0→25 °C, 1.5 h; then K_2CO_3 (2.5 equiv), MeOH, 25 °C, 18 h, 91%; i) 2-bromopropene (4.4 equiv), *t*BuLi (1.7 M in pentane, 8.0 equiv), THF, −78 °C, 5 min; then BF_3·Et_2O, 2 min; **9**, −78→−40 °C, 30 min, 83%; j) $pNO_2C_6H_4CO_2H$ (1.5 equiv), DEAD (1.5 equiv), Ph_3P (1.8 equiv), benzene, 0→25 °C, 18 h, 94%; k) DIBAL-H (1.0 M in hexanes, 2.5 equiv), CH_2Cl_2, −78 °C, 30 min, 96%; l) BOMCl (3.0 equiv), *i*Pr_2NEt (10 equiv), PhMe, 90 °C, 12 h; m) TBAF (1.0 M in THF, 15 equiv), 70 °C, 97% for two steps; n) NMO (1.5 equiv), TPAP (0.03 equiv), CH_2Cl_2/CH_3CN (9:1), 12 h, 96%; o) $TrisNHNH_2$ (1.8 equiv), THF, 5 h, 80%; p) *n*BuLi (2.5 M in hexanes, 2.1 equiv) THF, −78→−25 °C, 20 min; then I_2 (2.0 equiv), −78→−25 °C, 20 min, 90%; q) $pBrC_6H_4NCO$ (4.0 equiv), Et_3N (6.0 equiv), 25 °C; r) TBAF, THF, 25 °C, 74% for two steps. 4-DMAP = 4-dimethylaminopyridine, py = pyridine, TBDPS = *tert*-butyldiphenylsilyl, imid = imidazole, DIBAL-H = diisobutylaluminum hydride, NIS = *N*-iodosuccinimide, DEAD = diethylazodicarboxylate, TBAF = tetra-*n*-butylammonium fluoride, NMO = *N*-methylmorpholine-*N*-oxide, TPAP = tetra-*n*-propylammoniumperuthenate, Tris = triisopropylsulfonyl.

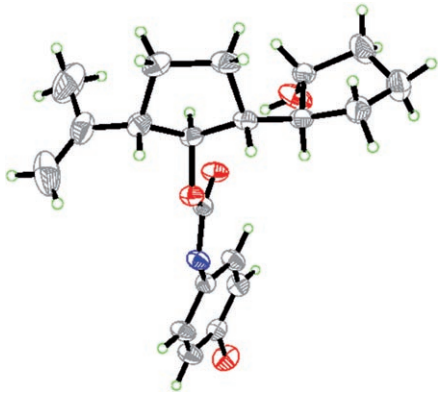


Figure 3. X-ray derived ORTEP drawing of **14** (thermal ellipsoids at 30% probability); gray C, green H, blue N, red O.

the crystalline *p*-bromophenyl carbamate **14** (m.p. 136–138 °C, EtOAc/hexanes) prepared from hydroxy compound **10** through reaction with *p*-bromophenyl isocyanate, followed by TBAF-induced desilylation, in 74% overall yield as shown in Scheme 1.

Scheme 2 outlines the construction of building block **3** starting from intermediate **15** (racemic)[8,9] or **15a** (enantiopure).[9] Thus, exposure of dihydroxy methyl ether **15** to B-bromocatecholborane, followed by selective monosilylation of the resulting triol (TIPSCl, imid) led to the corresponding primary TIPS ether (70% yield for the two steps), which was oxidized with IBX to afford diketone **16** (90% yield). Generation of the titanium enolate from **16** followed by addition of acetone (−92 °C) furnished the expected tertiary alcohol (d.r. ca. 9:1), which was silylated (TESOTf, 2,6-lut., −78→−40 °C) to afford bis(silyl) ether **17** (chromatographically separated) in 81% overall yield of the desired diastereomer for the two steps. The very low temperature (−92 °C) was necessary for the good stereoselectivity observed in this aldol reaction. The next step required stereoselective reduction of the two carbonyl groups within **17** to afford the desired 25α,26β dihydroxy compound, a prospect that, upon inspection of molecular models, looked good by virtue of the steric environment of these moieties. Indeed, exposure of **17** to $NaBH_4$ resulted in the formation of a single diol, from which the TES group was removed under mild desilylation conditions (PPTS, EtOH) to afford triol **18** in 85% overall yield from diketone **17**. Based on intelligence gathering from other experiments that will be revealed later, and in preparation for the samarium ring closure we had in mind, a SEM group was installed at C-26, a choice that left the acetonide moiety as the obvious guardian for the other two hydroxy groups. To this end, triol **18** was exposed to Ac_2O and 4-DMAP in CH_2Cl_2, conditions that acetylated selectively the C-26 hydroxy group (that turned out to be the most reactive of the three in our experience with these series of compounds), resulting in crystalline monoacetate **19** in 79% yield (m.p. 131–133 °C, hexanes). X-ray crystallographic analysis[10] of **19** (see ORTEP drawing, Figure 4) confirmed the relative stereochemistry of this intermediate as expected from its NMR spectroscopic data. Exposure of **19** to 2-methoxypropene in the presence of CSA afforded the corresponding

acetoxy acetonide (82% yield) which, after cleavage of the acetate group (MeMgBr, 50°C, 94% yield), was converted into its SEM derivative **20** (SEMCl, iPr$_2$NEt, 96% yield). Having installed the appropriate functionalities, and in their proper configurations on our growing tricyclic system, we then turned our attention to the construction of the remaining quaternary center at C-13. To this end, a Claisen rearrangement was called upon, with allyl enol ether **21** as the substrate. This substrate was expediently prepared from **20** by ozonolysis (O_3; Ph_3P, 96% yield), followed by O-allylation of the resulting aldehyde (KH, allyl chloride, 92% yield). Pleasantly, the anticipated Claisen rearrangement of **21** proceeded smoothly upon microwave irradiation at 200°C, furnishing the desired skeleton, which was swiftly reduced with $NaBH_4$ to afford alcohol **22**, in 88% yield for the two steps. The latter compound was then protected as the BOM ether (BOMCl, iPr$_2$NEt) and subjected to ozonolysis (O_3, Ph_3P) to give aldehyde **23** in 85% yield for the two steps. Finally, truncation by one carbon atom was accomplished by silyl enol ether formation (TBSCl, DBU) followed by a second ozonolysis (O_3, Ph_3P) to furnish the targeted aldehyde **3** in 97% overall yield for the two steps.

With both building blocks **2** and **3** readily available, their union and further elaboration to the reported vannusal B structure **1b** became the next task. As shown in Scheme 3, lithiation of the vinyl iodide **2** (tBuLi, −78→−40°C) followed by addition of racemic aldehyde **3** (−40→0°C) furnished a 1:1 diastereomeric mixture of products (**24** and its diastereoisomer, not shown) in 80% total yield. The two diastereoisomers were chromatographically separated and compared to the

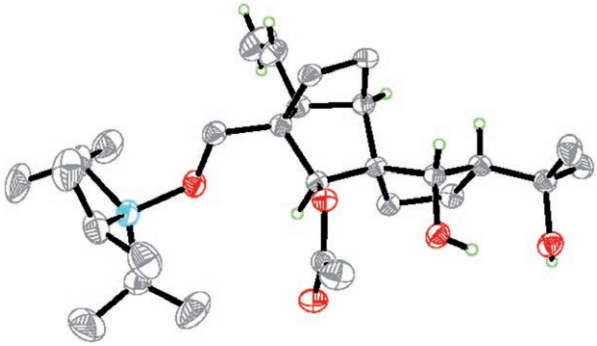
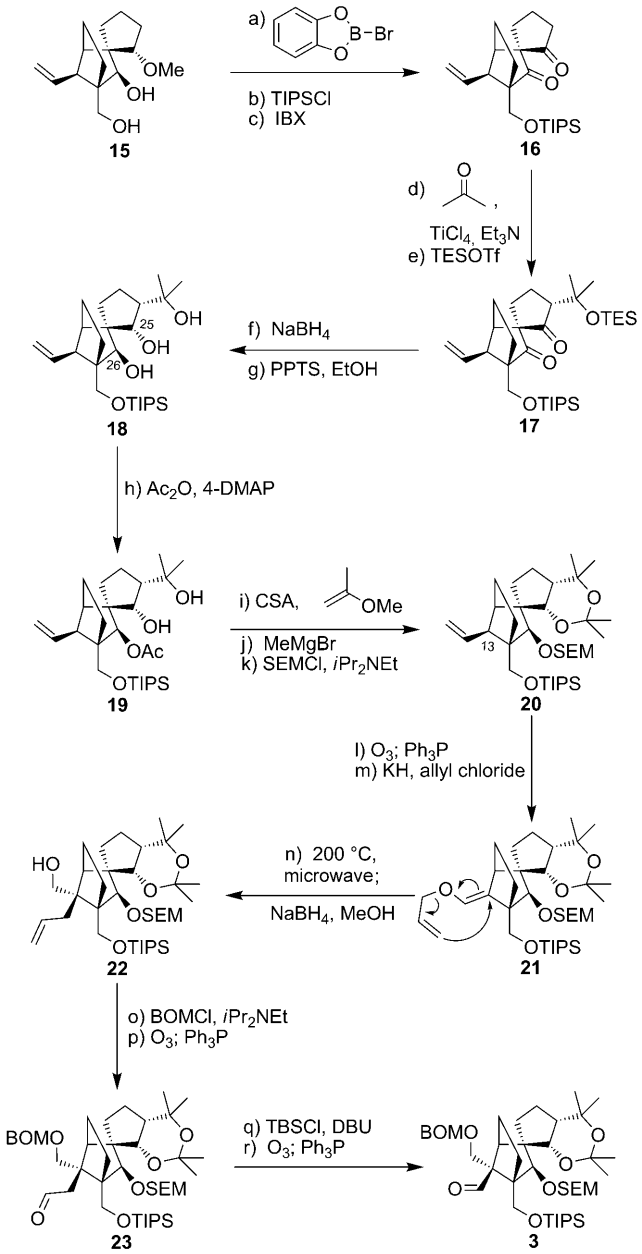


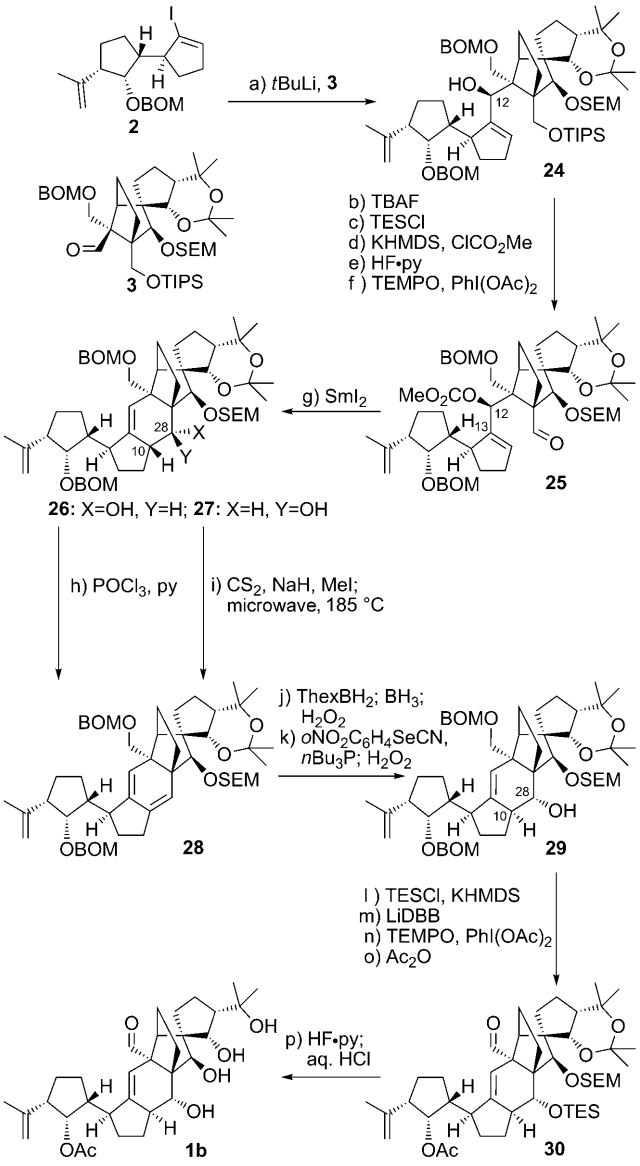
Figure 4. X-ray derived ORTEP drawing of **19** (thermal ellipsoids at 30% probability); gray C, green H, light blue Si, red O.



Scheme 2. Construction of aldehyde **3**. Reagents and conditions: a) B-Br-catecholborane (3.5 equiv), CH_2Cl_2, 25→50°C, 3 h; b) TIPSCl (1.5 equiv), imid (6.0 equiv), DMF, 24 h, 70% for two steps; c) IBX (3.0 equiv), DMSO, 50°C, 4 h, 90%; d) $TiCl_4$ (1.0 M in CH_2Cl_2, 1.2 equiv), Et_3N (3.0 equiv), CH_2Cl_2, −78→−30°C, 30 min; then acetone, −92°C, 12 h (d.r. 9:1); e) TESOTf (3.0 equiv), 2,6-lut. (5.0 equiv), −78→−40°C, 1 h, 81% for two steps; f) $NaBH_4$ (10 equiv), THF/MeOH (1:1), −10→25°C, 5 h; g) PPTS (0.2 equiv), EtOH, 25°C, 2 h, 85% for two steps; h) Ac_2O (20 equiv), 4-DMAP (0.1 equiv), Et_3N (40 equiv), CH_2Cl_2, 25°C, 18 h, 79%; i) 2-methoxypropene (20 equiv), CSA (1.0 equiv), CH_2Cl_2, −78→−30°C, 3 h, 82%; j) MeMgBr (50 equiv), PhMe, 50°C, 8 h, 94%; k) SEMCl (10 equiv), iPr$_2$NEt (30 equiv), TBAI (1.0 equiv), CH_2Cl_2, 50°C, 48 h, 96%; l) 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, 96%; m) KH (10 equiv), allyl chloride (20 equiv), HMPA (5.0 equiv), DME, −10→25°C, 3 h, 92%; n) iPr$_2$NEt (1.0 equiv), 1,2-dichlorobenzene, 200°C (microwave), 20 min; then $NaBH_4$ (20 equiv), MeOH, 1 h, 25°C, 88% for two steps; o) BOMCl (6.0 equiv), iPr$_2$NEt (15 equiv), CH_2Cl_2, 50°C, 12 h; p) 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, 85% for two steps; q) TBSCl (10 equiv), DBU (20 equiv), CH_2Cl_2, 25°C, 36 h; r) 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% for two steps. TES = triethylsilyl, 2,6-lut. = 2,6-dimethylpyridine, PPTS = pyridinium p-toluenesulfonate, CSA = camphorsulfonic acid, HMPA = hexamethylphosphoramide, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, DME = 1,2-dimethoxyethane, IBX = o-iodoxybenzoic acid, OTf = trifluoromethanesulfonate, TBAI = tetra-n-butylammonium iodide, TBSCl = $tert$-butyldimethylsilyl chloride.

single (and diastereomerically desired) product obtained from the coupling reaction in which enantiopure aldehyde (+)-**31** (closely related to aldehyde **3** having only the SEM and acetonide groups flipped, Scheme 4) was used to reveal the identity of the desired diastereoisomer within the above mixture. The coupling products derived from the two aldehydes [(±)-**3** and (+)-**31**] were correlated downstream, and their structures unambiguously assigned indirectly by X-ray crystallographic analysis of a crystalline derivative (see below). This identification was important since (±)-**3** was easier to obtain than its enantiopure counterpart, and was, therefore, employed at this juncture for practical reasons. The β stereochemistry of the newly generated stereocenter in **24** (C-12) was expected on steric grounds (addition of the lithio reagent to the less hindered face of the chelated aldehyde) and was confirmed by nuclear Overhauser effect (NOE) studies. At this stage, our designed strategy called for a SmI_2-induced ring closure involving radical anion generation at the aldehyde site, followed by attack on the adjacent olefinic bond and expulsion of a leaving group at C-12 with concomitant migration of the double bond to the C-11–C-12 position.[11]

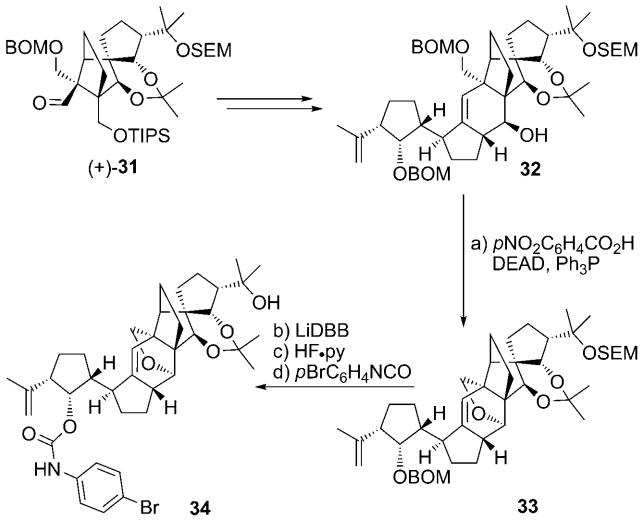
It was to this end that the following four-step sequence was carried out from hydroxy compound **24** to the aldehyde carbonate **25**: 1) exchange of the TIPS moiety (TBAF, 25 °C, 98% yield) for the more labile TES group (TESCl, imid, 99% yield); 2) carbonate formation at C-12 (KHMDS, $ClCO_2Me$); 3) selective removal of the TES group (HF·py, 92% for the two steps); and 4) oxidation of the liberated primary hydroxy group to the aldehyde (TEMPO, $PhI(OAc)_2$, 98% yield). The final ring of the desired polycyclic skeleton was then forged by treatment of substrate **25** with a solution of SmI_2 in THF in the presence HMPA at −10→25 °C, yielding a mixture of two diastereomeric alcohols (differing at C-28), **26** (28% yield) and **27** (52% yield), which were chromatographically separated. The stereochemical assignments for these two compounds were based on NMR spectroscopic analysis, particularly NOE studies. Faced with the unpleasant stereochemical outcome of this reaction, which otherwise performed admirably, we decided to eradicate the two newly generated stereocenters (at C-10 and C-28) through dehydration, and reconstruct them in their proper configurations by exploiting the reactivity preferences of the resulting diene system. Triene **28** was secured from either isomer **26** or **27**, each precursor, however, requiring its own path. Thus, treatment of isomer **26** (in which the OH group resides *anti* to H-10) with $POCl_3$ (py, 60 °C) led directly to **28** (81% yield), whereas isomer **27** (in which the OH group is *syn* to H-10) required conversion into its xanthate first (NaH, CS_2, MeI, 0→25 °C), and then *syn* elimination, a process that proceeded smoothly upon microwave irradiation at 185 °C (92% overall yield).[12] The next hurdle to be overcome was the regio- and stereoselective hydration of the C-10–C-28 olefinic bond in



Scheme 3. Completion of the synthesis of structure **1b**. Reagents and conditions: a) **2** (1.3 equiv), *t*BuLi (2.6 equiv), THF, −78→−40 °C, 30 min; then **3** (1.0 equiv), −40→0 °C, 20 min, 80%; b) TBAF (1.0 M in THF, 5.0 equiv), THF, 25 °C, 1 h, 98%; c) TESCl (1.5 equiv), imid (5.0 equiv), CH_2Cl_2, 25 °C, 1 h, 99%; d) KHMDS (0.5 M in PhMe, 3.0 equiv), $ClCO_2Me$ (5.0 equiv), Et_3N (5.0 equiv), THF, −78→25 °C, 2 h; e) HF·py/py (1:4), 0→25 °C, 12 h, 88% for two steps; f) TEMPO (1.0 equiv), $PhI(OAc)_2$ (3.0 equiv), CH_2Cl_2, 25 °C, 24 h, 98%; g) SmI_2 (0.1 M in THF, 5.0 equiv), HMPA (15 equiv), THF, −10→25 °C, 30 min, 80% (**26**: 28%, **27**: 52%); h) $POCl_3$ (60.0 equiv), py, 60 °C, 3 h, 81%; i) CS_2 (8.0 equiv), NaH (6.0 equiv), THF, 0→25 °C, 30 min; then CH_3I (12 equiv), 0→25 °C, 3 h; then 185 °C (microwave), 1,2-dichlorobenzene, 15 min, 92%; j) $ThexBH_2$ (5.0 equiv), THF, −10→25 °C, 1 h; then BH_3·THF (15 equiv), 0→25 °C, 30 min; then 30% H_2O_2/3 N NaOH (1:1), 25→40 °C, 1 h; 65% (1:1.3 mix); k) $oNO_2C_6H_4SeCN$ (2.0 equiv), nBu_3P (6.0 equiv), py (12 equiv), THF, 25 °C; then 30% H_2O_2, 0→25 °C, 67%; l) KHMDS (0.5 M in PhMe, 5.0 equiv), TESCl (5.0 equiv), Et_3N (8.0 equiv), THF, −78→25 °C, 30 min, 94%; m) LiDBB (excess), THF, −78→−50 °C, 30 min, 84%; n) TEMPO (1.0 equiv), $PhI(OAc)_2$ (3.0 equiv), CH_2Cl_2, 25 °C, 24 h, 88%; o) Ac_2O (30 equiv), Et_3N (30 equiv), 4-DMAP (1.0 equiv), CH_2Cl_2, 25 °C, 12 h, 100%; p) HF·py/THF (1:4), 25 °C, 3 h; then 3 N aq HCl/THF (1:3), 25 °C, 6 h, 80%. KHMDS = potassium hexamethyldisilazide, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical, LiDBB = lithium di-*tert*-butylbiphenyl, $ThexBH_2$ = 2,3-dimethyl-2-butylborane.

the presence of the other two within intermediate **28**. An expedient tactic to solve this seemingly thorny problem was devised based on the unique steric environment of each olefinic bond within this substrate. Thus, hydroboration of triene **28**, first with $ThexBH_2$ (terminal olefin, two diastereoisomers), and then with BH_3·THF (C-10–C-28 olefin, single diastereisomer) afforded, after the usual oxidative work-up, a mixture of two diastereomeric diols (ca. 1:1.3, 65% yield). This mixture was then dehydrated through *syn* elimination (H_2O_2, 67% overall yield) of the primary *o*-nitrophenyl selenides which were selectively generated from the diol mixture ($oNO_2C_6H_4SeCN$, nBu_3P).[13] The desired configurations at C-10 and C-28 within the newly obtained hydroxy compound (**29**) were confirmed by NOE studies. Having reached **29** with all stereochemistry in place as required, only a short path now separated it from the targeted molecule. The requisite aldehyde and acetate moieties were installed through a short sequence [1) KHMDS, TESCl, 94% yield; 2) LiDBB, THF, −78→−50°C, 84% yield; 3) TEMPO, PhI(OAc)$_2$, 88% yield; and 4) Ac_2O, 4-DMAP, Et_3N, 100% yield] to afford advanced intermediate **30**. Global deprotection of **30** through the sequential action of HF·py and aqueous HCl in the same pot furnished the coveted structure **1b** in 80% yield. The spectroscopic data of the synthesized compound, however, although similar, did not match those reported[1] for the naturally occurring vannusal B.

Lest there was any doubt about our synthesized structure **1b**, a serendipitous discovery allowed further support for its structural identity. Thus, activation of alcohol **32** [Scheme 4; obtained from (+)-**31** through a similar sequence as that shown in Scheme 3] under Mitsunobu conditions (attempted for inversion of configuration) resulted in the formation of the polycyclic compound **33** (88% yield based on recovered material). The new, and unexpected, ring within **33** was apparently formed by intramolecular attack of the OBOM group upon the initially generated reactive intermediate in each of these reactions. Proximity combined with rigidity must be responsible for this unusual, but facile process. Sequential removal of the BOM (LiDBB) and SEM (HF·py) groups gave the corresponding diol, which reacted with *p*-bromophenyl isocyanate to afford *p*-bromophenyl carbamate **34** in 70% overall yield. The latter compound crystallized in beautiful needles from EtOAc/hexanes, m.p. 180–182°C. X-ray crystallographic analysis of these crystals (see ORTEP drawing, Figure 5)[14] provided unambiguous confirmation of its structure and those of its precursors.



Scheme 4. Synthesis of crystalline derivative **34**. Reagents and conditions: a) DEAD (10 equiv), Ph_3P (10 equiv), $pNO_2C_6H_4CO_2H$ (10 equiv), benzene, 60°C, 2 h, 88% based on recovered starting material; b) LiDBB, THF, −78→−50°C; c) HF·py/THF, 25°C, 4 h; d) $pBrC_6H_4NCO$ (3 equiv), Et_3N, 40°C, 70% for three steps.

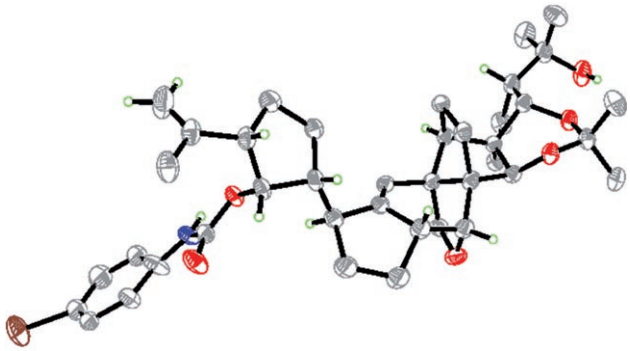


Figure 5. X-ray derived ORTEP drawing of **34** (thermal ellipsoids at 30% probability); gray C, green H, brown Br, blue N, red O.

The described chemistry provides a highly convergent approach to the vannusal molecular framework, including the originally proposed structure of vannusal B (**1b**). It also proved that this structure (**1b**) does not represent the true molecular identities of the vannusals, precipitating a puzzle that still remains to be solved.

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