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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* 

**Natural Products** 



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

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.<sup>[1,2]</sup> Herein we report the total synthesis of structure **1b** that proved that it does not represent the true structure of vannusal B.

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.

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*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<sub>3</sub> (py, 90°C) furnished conjugated diene 5 (97% yield),<sup>[3]</sup> which was regio- and stereoselectively converted into the new meso diol 6 by a hydroboration-oxidation process (CyBH<sub>2</sub>; H<sub>2</sub>O<sub>2</sub>, NaOH, 51% yield). The latter compound was then desymmetrized through the enantioselective hydrolytic action of Lipase Amano PS<sup>[4]</sup> on its bis-acetate (prepared in quantitative yield by reaction of 6 with Ac<sub>2</sub>O 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<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 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<sub>2</sub>O), and then ring closure (K<sub>2</sub>CO<sub>3</sub>, MeOH) to give  $\beta$ -epoxide 9 in 91% overall yield. This epoxide was then regio- and stereoselectively opened with 2-lithiopropene (generated from the corresponding bromide and tBuLi) in the presence of BF<sub>3</sub>·Et<sub>2</sub>O to afford hydroxy compound **10** (83%) yield), whose stereochemistry was inverted through application of a Mitsunobu (pNO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H, Ph<sub>3</sub>P, DEAD)<sup>[5]</sup>/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, *i*Pr<sub>2</sub>NEt) 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<sub>2</sub>, 80% yield). Finally, the targeted vinyl iodide **2** emerged in 90% yield through a Shapiro reaction<sup>[6]</sup> of hydrazone 13 (nBuLi,  $I_2$ ). The relative and absolute stereochemistry of this series of compounds was confirmed by X-ray crystallographic analysis (see ORTEP drawing, Figure 3)<sup>[7]</sup> of

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Communications



Scheme 1. Enantioselective construction of vinyl iodide 2. Reagents and conditions: a) POCl<sub>3</sub> (2.2 equiv), py, 90 °C, 2 h, 97%; b) BH<sub>3</sub>·THF (2.5 equiv), cyclohexene (2.5 equiv),  $-40 \rightarrow 0$  °C, 2 h; then 5,  $-40 \rightarrow$ 25°C, 12 h; then 50°C, 30 min; then 30% H<sub>2</sub>O<sub>2</sub>/3 N NaOH (2:1 v/v), -50→50°C, 12 h, 51%; c) Ac<sub>2</sub>O (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) TBDPSC (1.2 equiv), imid (3.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 12 h, 93 %; f) DIBAL-H (1.0 м in hexanes, 2.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -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<sub>2</sub>O (4:1),  $0\rightarrow$  25 °C, 1.5 h; then K<sub>2</sub>CO<sub>3</sub> (2.5 equiv), MeOH, 25 °C, 18 h, 91%; i) 2-bromopropene (4.4 equiv), tBuLi (1.7 м in pentane, 8.0 equiv), THF, -78 °C, 5 min; then BF<sub>3</sub>·Et<sub>2</sub>O, 2 min; 9,  $-78 \rightarrow -40$  °C, 30 min, 83%; j)  $pNO_2C_6H_4CO_2H$  (1.5 equiv), DEAD (1.5 equiv),  $Ph_{3}P$  (1.8 equiv), benzene,  $0 \rightarrow 25$  °C, 18 h, 94%; k) DIBAL-H (1.0 м in hexanes, 2.5 equiv), CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 30 min, 96%; I) BOMCI (3.0 equiv), *i*Pr<sub>2</sub>NEt (10 equiv), PhMe, 90°C, 12 h; m) TBAF (1.0 м in THF, 15 equiv), 70°С, 97% for two steps; n) NMO (1.5 equiv), TPAP (0.03 equiv), CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>CN (9:1), 12 h, 96%; o) TrisNHNH<sub>2</sub> (1.8 equiv), THF, 5 h, 80%; p) *n*BuLi (2.5 м in hexanes, 2.1 equiv) THF,  $-78 \rightarrow -25$  °C, 20 min; then I<sub>2</sub> (2.0 equiv), -78 --25 °C, 20 min, 90%; q) pBrC<sub>6</sub>H<sub>4</sub>NCO (4.0 equiv), Et<sub>3</sub>N (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)<sup>[8,9]</sup> or 15a (enantiopure).<sup>[9]</sup> Thus, exposure of dihydroxy methyl ether **15** to Bbromocatecholborane, 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 silvlated (TESOTf, 2,6-lut.,  $-78 \rightarrow -40$  °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  $25\alpha$ ,  $26\beta$  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<sub>4</sub> 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<sub>2</sub>O and 4-DMAP in CH<sub>2</sub>Cl<sub>2</sub>, 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<sup>[10]</sup> 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

. B−Br ОH b) TIPSCI c) IBX 'nн OTIPS 16 15 d) TiCl<sub>4.</sub> Et<sub>3</sub>N e) TESOTf OTES ο⊢ f) NaBH<sub>4</sub> ŐН g) PPTS, EtOH он OTIPS OTIPS 17 18 h) Ac<sub>2</sub>O, 4-DMAP юн i) CSA. OMe ŐН 'n j) MeMgBr k) SEMCl, *i*Pr<sub>2</sub>NEt OSEM OAc OTIPS OTIPS 19 20 I) O<sub>3</sub>; Ph<sub>3</sub>P m) KH, allyl chloride n) 200 °C microwave 'n OSEM NaBH<sub>4</sub>, MeOH OSEM OTIPS OTIPS 22 21 o) BOMCI, *i*Pr<sub>2</sub>NEt p) O<sub>3</sub>; Ph<sub>3</sub>P q) TBSCI, DBU BOMO `C BOMO r) O<sub>3</sub>; Ph<sub>3</sub>P Ć Ć OSEM OSEM 0= ő OTIPS OTIPS 23 3

acetoxy acetonide (82% yield) which, after cleavage of the acetate group (MeMgBr, 50°C, 94% yield), was converted

OSEM OTIPS 23 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) TIPSCI (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<sub>4</sub> (1.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 1.2 equiv), Et<sub>3</sub>N (3.0 equiv),  $CH_2Cl_2$ ,  $-78 \rightarrow -30°C$ , 30 min; then acetone, -92°C, 12 h (d.r. 9:1); e) TESOTf (3.0 equiv), 2,6-lut. (5.0 equiv),  $-78 \rightarrow -40°C$ , 1 h, 81% for two steps; f) NaBH<sub>4</sub> (10 equiv), THF/ MeOH (1:1),  $-10 \rightarrow 25°C$ , 5 h; g) PPTS (0.2 equiv), EtOH, 25°C, 2 h, 85% for two steps; h) Ac<sub>2</sub>O (20 equiv), 4-DMAP (0.1 equiv), Et<sub>3</sub>N

(40 equiv),  $CH_2Cl_2$ , 25 °C, 18 h, 79 %; i) 2-methoxypropene (20 equiv), CSA (1.0 equiv),  $CH_2Cl_2$ ,  $-78 \rightarrow -30 °C$ , 3 h, 82 %; j) MeMgBr (50 equiv), PhMe, 50 °C, 8 h, 94 %; k) SEMCI (10 equiv),  $iPr_2NEt$ (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),  $-78 \rightarrow$ 25 °C, 1 h, 96 %; m) KH (10 equiv), allyl chloride (20 equiv), HMPA



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

into its SEM derivative 20 (SEMCl, iPr2NEt, 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<sub>3</sub>; Ph<sub>3</sub>P, 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<sub>4</sub> to afford alcohol 22, in 88% yield for the two steps. The latter compound was then protected as the BOM ether (BOMCl,  $iPr_2NEt$ ) and subjected to ozonolysis (O<sub>3</sub>, Ph<sub>3</sub>P) 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 (*t*BuLi,  $-78 \rightarrow -40$  °C) followed by addition of racemic aldehyde 3 ( $-40 \rightarrow 0$  °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

(5.0 equiv), DME,  $-10 \rightarrow 25$  °C, 3 h, 92%; n) *i*Pr<sub>2</sub>NEt (1.0 equiv), 1,2dichlorobenzene, 200 °C (microwave), 20 min; then NaBH<sub>4</sub> (20 equiv), MeOH, 1 h, 25 °C, 88% for two steps; o) BOMCI (6.0 equiv), *i*Pr<sub>2</sub>NEt (15 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 50 °C, 12 h; p) O<sub>3</sub>, py (1.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1:1), -78 °C; then Ph<sub>3</sub>P (5.0 equiv),  $-78 \rightarrow 25$  °C, 1 h, 85% for two steps; q) TBSCI (10 equiv), DBU (20 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 36 h; r) O<sub>3</sub>, py (1.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>/MeOH (1:1), -78 °C; then Ph<sub>3</sub>P (5.0 equiv),  $-78 \rightarrow 25$  °C, 1 h, 97% for two steps. TES = triethylsilyl, 2,6-lut. = 2,6dimethylpyridine, PPTS = pyridinium *p*-toluenesulfonate, CSA = camphorsulfonic acid, HMPA = hexamethylphosphoramide, DBU = 1,8diazabicyclo[5.4.0]undec-7-ene, DME = 1,2-dimethoxyethane, IBX = *o*-iodoxybenzoic acid, OTf = trifluoromethanesulfonate, TBAI = tetra-*n*-butylammonium iodide, TBSCI = *tert*-butyldimethylsilyl chloride.

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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  $[(\pm)-3]$  and (+)-**31**] were correlated downstream,



Scheme 3. Completion of the synthesis of structure 1b. Reagents and conditions: a) 2 (1.3 equiv), tBuLi (2.6 equiv), THF,  $-78 \rightarrow -40^{\circ}$ C, 30 min; then 3 (1.0 equiv),  $-40 \rightarrow 0^{\circ}$ 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<sub>2</sub>Cl<sub>2</sub>, 25 °C, 1 h, 99%; d) KHMDS (0.5 m in PhMe, 3.0 equiv), ClCO<sub>2</sub>Me (5.0 equiv), Et<sub>3</sub>N (5.0 equiv), THF,  $-78 \rightarrow 25^{\circ}$ C, 2 h; e) HF·py/py (1:4),  $0 \rightarrow 25^{\circ}$ C, 12 h, 88% for two steps; f) TEMPO (1.0 equiv), PhI(OAc)<sub>2</sub> (3.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 24 h, 98%; g) Sml<sub>2</sub> (0.1 m in THF, 5.0 equiv), HMPA (15 equiv), THF,  $-10 \rightarrow 25^{\circ}$ C, 30 min, 80% (26: 28%, 27: 52%); h) POCl<sub>3</sub> (60.0 equiv), py, 60°C, 3 h, 81%; i) CS<sub>2</sub> (8.0 equiv), NaH (6.0 equiv), THF,  $0 \rightarrow 25^{\circ}$ C, 30 min; then CH<sub>3</sub>I (12 equiv),  $0 \rightarrow 25^{\circ}$ C, 3 h; then 185 °C (microwave), 1,2-dichlorobenzene, 15 min, 92%; j) ThexBH<sub>2</sub> (5.0 equiv), THF,  $-10 \rightarrow 25^{\circ}$ C, 1 h;

and their structures unambiguously assigned indirectly by Xray crystallographic analysis of a crystalline derivative (see below). This identification was important since  $(\pm)$ -**3** was easier to obtain than its enantiopure counterpart, and was, therefore, employed at this juncture for practical reasons. The  $\beta$  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<sub>2</sub>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.<sup>[11]</sup>

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<sub>2</sub>Me); 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)<sub>2</sub>, 98% yield). The final ring of the desired polycyclic skeleton was then forged by treatment of substrate 25 with a solution of SmI2 in THF in the presence HMPA at  $-10 \rightarrow 25$  °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<sub>3</sub> (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<sub>2</sub>, MeI,  $0 \rightarrow 25$  °C), and then syn elimination, a process that proceeded smoothly upon microwave irradiation at 185°C (92% overall yield).<sup>[12]</sup> The next hurdle to be overcome was the regio- and stereoselective hydration of the C-10-C-28 olefinic bond in

then BH<sub>3</sub>·THF (15 equiv),  $0 \rightarrow 25$  °C, 30 min; then 30% H<sub>2</sub>O<sub>2</sub>/3 N NaOH (1:1), 25 $\rightarrow$ 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<sub>2</sub>O<sub>2</sub>,  $0 \rightarrow 25$  °C, 67%; l) KHMDS (0.5 M in PhMe, 5.0 equiv), TESCI (5.0 equiv), Et<sub>3</sub>N (8.0 equiv), THF,  $-78 \rightarrow 25$  °C, 30 min, 94%; m) LiDBB (excess), THF,  $-78 \rightarrow -50$  °C, 30 min, 84%; n) TEMPO (1.0 equiv), PhI(OAc)<sub>2</sub> (3.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 24 h, 88%; o) Ac<sub>2</sub>O (30 equiv), Et<sub>3</sub>N (30 equiv), 4-DMAP (1.0 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 25 °C, 12 h, 100%; p) HF.py/THF (1:4), 25 °C, 3 h; then 3 N aq HCI/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<sub>2</sub> = 2,3-dimethyl-2-butylborane.

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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<sub>2</sub> (terminal olefin, two diastereoisomers), and then with BH<sub>3</sub>·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<sub>2</sub>O<sub>2</sub>, 67% overall yield) of the primary *o*-nitrophenyl selenides which were selectively generated from the diol mixture (oNO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>SeCN, nBu<sub>3</sub>P).<sup>[13]</sup> 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, TESCI, 94% yield; 2) LiDBB, THF,  $-78 \rightarrow -50$  °C, 84% yield; 3) TEMPO, PhI-(OAc)<sub>2</sub>, 88% yield; and 4) Ac<sub>2</sub>O, 4-DMAP, Et<sub>3</sub>N, 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<sup>[1]</sup> 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



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,  $-78 \rightarrow -50$ °C; c) HF·py/THF, 25°C, 4 h; d)  $pBrC_6H_4NCO$  (3 equiv), Et<sub>3</sub>N, 40°C, 70% for three steps.

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. Xray crystallographic analysis of these crystals (see ORTEP drawing, Figure 5)<sup>[14]</sup> provided unambiguous confirmation of its structure and those of its precursors.



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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