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An expedient entry into the fused polycyclic skeleton of vannusal A†‡

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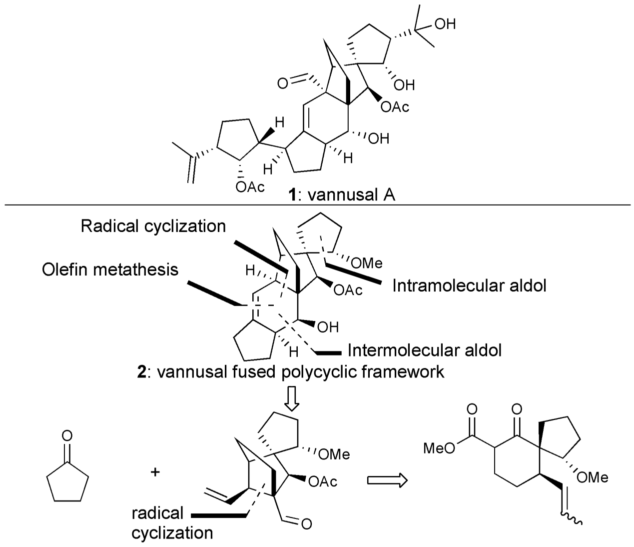
The synthesis of the fused polycyclic carbon framework of vannusal A is described; key features include inter- and intramolecular aldol reactions, a Mn(III) initiated radical cyclization, and a ring-closing olefin metathesis reaction.

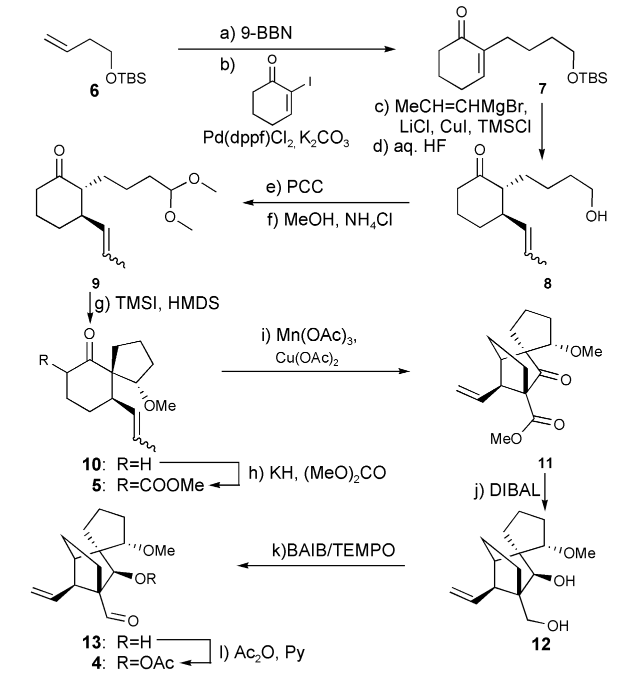
In 1999, a highly unusual triterpene, termed vannusal A (**1**, Scheme 1), was reported by the Pietra group.[1] Isolated from the tropical strains of the marine ciliate *Euplotes vannus*, **1** possesses a 30-carbon backbone comprising seven rings and thirteen stereogenic centers of which three are quaternary. Whereas various biosynthetic pathways for the generation of **1** from squalene can be imagined,[1] its total synthesis in a laboratory setting can be considered rather challenging and most likely requiring special strategies and tactics. Specifically, the fused polycyclic carbon core of vannusal A was deemed from the very outset as the most severe hurdle to be overcome before a total synthesis could be realized. We, therefore, initially focused our efforts on the construction of model system **2** (Scheme 1) representing the basic framework of the molecule. In this communication, we report a facile entry into the fused polycyclic carbon skeleton of vannusal A by a convergent strategy featuring a number of selective transformations that will hopefully pave the way for its eventual total synthesis.

Inspection of structure **2** revealed the strategic bond disconnections indicated in Scheme 1 as particularly productive in unraveling potential starting building blocks for its construction. Thus, an intermolecular aldol process, in conjunction with an olefin metathesis reaction, allowed the disassembly of **2** into key intermediates **3** and **4** as potential precursors. The convergent strategy suggested by these two disconnections was advanced further by tracing tricycle **4** to spiro system **5** *via* a key radical-induced ring closure. It was anticipated that the projected cascade radical cyclization of **5** to **4** could be initiated by $Mn(OAc)_3$ whereas a Mukaiyama-type aldol reaction was reserved for the construction of the required spiro ketone **5**.

The highly functionalized and strained norbornane derivative **4** was synthesized as delineated in Scheme 2. The successful route to this intermediate began with a one-pot, tandem sequence involving regioselective hydroboration of olefinic substrate **6** with 9-BBN (for abbreviations of reagents and protecting groups, see the legends in Schemes 2 and 3) followed by coupling of the resulting borane under Suzuki conditions ($Pd[dppf]Cl_2$, K_2CO_3, 80 °C) with the required iodo-ketone, leading to enone **7** in 84% overall yield.[2] Conjugate addition of a propenyl group to **7** proceeded by addition of the correspond-



Scheme 1 Structure of vannusal A (**1**), fused polycyclic skeleton **2**, and retrosynthetic analysis of the latter (**2**).



Scheme 2 Preparation of the key keto-aldehyde intermediate **4**: (a) 9-BBN (1.2 equiv.), THF, 75 °C, 2 h; (b) $Pd[dppf]Cl_2$ (1 mol%), aq. K_2CO_3 (4.0 equiv.), THF, 80 °C, 4 h, 84%; (c) LiCl (0.2 equiv.), CuI (0.1 equiv.), TMSCl (1.5 equiv.), THF, −20 °C, 0.5 h; then MeCH=CHMgBr (1.2 equiv.), THF, −20 °C, 2 h; (d) aq. HF (2.0 equiv.), MeCN, 25 °C, 2 h, 71%; (e) PCC (1.5 equiv.), CH_2Cl_2, 25 °C, 1 h, 89%; (f) NH_4Cl (0.1 equiv.), MeOH, 50 °C, 2.5 h, 95%; (g) HMDS (1.5 equiv.), CH_2Cl_2, 0 °C, 0.5 h; then TMSI (1.3 equiv.), CH_2Cl_2, 1 h, 50%, (h) KH (3.0 equiv.), $(MeO)_2CO$ (20.0 equiv.), THF, 85 °C, 4 h, 95%, (i) $Mn(OAc)_3$ (3.0 equiv.) $Cu(OAc)_2$ (2.0 equiv.), HOAc, 80 °C, 1 h, 76%; (j) DIBAL (4.0 equiv.), THF, −78 to 0 °C, 5 h, 91%; (k) BAIB (2.0 equiv.), TEMPO (0.1 equiv.),CH_2Cl_2, 25 °C, 12 h, 75%; (l) Ac_2O (10.0 equiv.), pyridine, 50 °C, 3 h, 71%. 9-BBN = 9-borabicyclo[3.3.1]nonane, dppf = diphenylphosphino ferrocene, TMS = trimethylsilyl, DIBAL = diisobutylaluminium hydride, BAIB = [bis(acetoxy)iodo]benzene, TEMPO = 2,2,6,6 tetramethyl-1-piperidinyloxyl.

† Electronic supplementary information (ESI) available: selected physical data for compounds **11** and **2**. See http://www.rsc.org/suppdata/cc/b2/b208234a/
‡ Dedicated to Professor Herbert C. Brown on the occasion of his 90th birthday.

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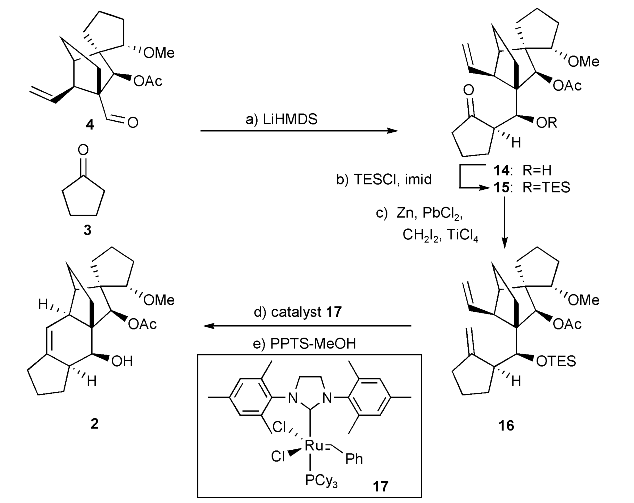

Scheme 3 Synthesis of vannusal A′s polycyclic skeleton (**2**): (a) **3**, LiHMDS (2.2 equiv.),THF, −78 °C, 1 h; then **4**, 1 h, −78 °C, 65%; (b) TESCl (1.2 equiv.), imidazole (2.5 equiv.), DMAP (0.5 equiv.), DMF, 25 °C, 36 h, 72%; (c) Zn (10.0 equiv.), $PbCl_2$ (0.01 equiv.), TMSCl (0.1 equiv.), CH_2I_2 (20.0 equiv.), THF, 25 °C, 0.5 h; then $TiCl_4$ (3.0 equiv.), 5 h, 88%; (d) catalyst 17, (0.3 equiv.) CH_2Cl_2, 50 °C, 12 h, 84%; (e) PPTS (0.3 equiv.), MeOH, CH_2Cl_2, 25 °C, 6 h, 91%; LiHMDS = lithium salt of 1,1,1,3,3,3-hexamethyldisilazane, TES = triethylsilyl, PPTS = pyridinium *p*-toluenesulfonate.

ing Grignard reagent under modified Kharasch[3] conditions (CuI–LiCl) to afford the corresponding enolate, which was trapped with TMSCl as the silyl enol ether.[4] Treatment of the latter product with aq. HF removed both silyl groups and furnished intermediate **8**, with the *trans* arrangement of the two appendages on the six-membered ring, as a mixture of inconsequential geometrical isomers in 71% overall yield. Oxidation of the primary alcohol in **8** with PCC led to the corresponding keto-aldehyde (89% yield), whose aldehyde function was then selectively converted to a dimethoxy acetal **9** by treatment with catalytic amounts of NH_4Cl in refluxing MeOH (95% yield) thereby setting the stage for the crucial intramolecular spirocyclization *via* a Mukaiyama-type aldol reaction. Gratifyingly, upon exposure of acetal **9** to excess TMSI in the presence of HMDS, cyclization proceeded to afford the coveted spiro compound **10** in 50% yield as a single stereoisomer (except for the olefin geometry which was maintained as a mixture).[5] With the first quaternary center fixed in intermediate **10**, we then turned our attention to the introduction of the second such motif. Thus, refluxing spirocycle **10** in THF with excess KH and $(MeO)_2CO$ afforded, quantitatively, keto-ester **5** as a mixture of two diastereomers (95% total yield). Noteworthy is the fact that, just as in the case of the geometrical isomerism, the stereochemistry of the ester group in **5** was irrelevant to the stereochemical outcome of the pending ring closure. Indeed, treatment of the latter compound (**5**) with $Mn(OAc)_3$ and $Cu(OAc)_2$ in hot acetic acid (80 °C) according to the Snider protocol furnished the expected keto-ester **11** in 76% yield as a single diastereomer *via* the anticipated radical pathway.[6] The next step toward **4** was the reduction of **11** to the corresponding diol, an objective which was accomplished stereoselectively with DIBAL. Much to our delight, the resulting relative stereochemistry within **12** correlated with the required configuration of **1** as evidenced by the observed nOe enhancements (see Fig. 1). The primary hydroxyl of **12** was selectively oxidized by the BAIB-TEMPO protocol[7] to furnish aldehyde **13** in 75% overall yield. Subsequent acetylation (Ac_2O, py) of the free secondary alcohol furnished the protected aldehyde **4** in 72% yield.

With the required fragment **4** readily available, attention was then focused on coupling the two fragments and then executing the final elaborations to the target structure, as shown in Scheme 3. Thus, treatment of cyclopentanone (**3**) with excess LiHMDS in THF at −78 °C, followed by addition of aldehyde **4**, led to the

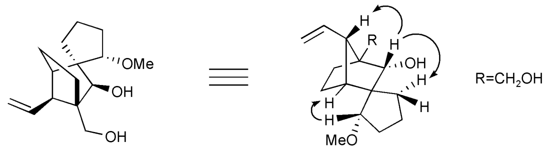

Fig. 1 Key nOe enhancements for diol 14.

isolation of a diastereomerically pure aldol product (**14**) in 65% yield (based on **4**) whose spectroscopic data were consistent with the opposite stereochemistry for the hydroxyl group as required for vannusal A (*anti* as opposed to the desired *syn*). Since this stereochemical outcome could, in principle, be rectified later on in the sequence through standard chemistry, we proceeded to the next stage which required protection of the newly generated hydroxyl group as a TES ether (TESCl, imidazole, 72% yield) furnishing protected diol **15**. Concerned with potential epimerization and/or elimination problems during the pending olefination of the cyclopentanone moiety in **15** under the standard Wittig conditions, we turned to a modified Takai protocol[8] in which the action of the obligatory reagents (Zn, CH_2I_2, and $TiCl_4$) was enhanced by the addition of catalytic amounts of $PbCl_2$ and TMSCl. This reaction performed admirably in this instance to afford the desired olefin (**16**) in 88% yield.[9] Pleasantly, exposure of **16** to Grubbs' second generation catalyst **17** formed the missing cyclohexene ring and subsequent PPTS promoted desilylation led to the targeted vannusal skeleton **2** in 76% yield.[10] With the complete fused polycyclic framework in hand, our attention was finally turned to deducing the global relative stereochemistry of the synthesized molecule. As shown in Fig. 2, all of the stereogenic centers of **2**‡ correspond, as indicated by the nOe enhancements, to that of **1**, except for the free hydroxyl group which resides in the pseudo-equatorial position.

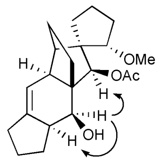

Fig. 2 Key nOe enhancements for polycycle **2**.

The described synthesis of vannusal A's fused polycyclic skeleton represents a novel approach to this natural product and demonstrates the power of modern synthetic technologies to construct complex molecular architectures. Efforts toward implementing this strategy to effect the total synthesis of vannusal A and B are now under way.

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