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# Studies directed toward the synthesis of viridenomycin. Route 2: a second generation approach

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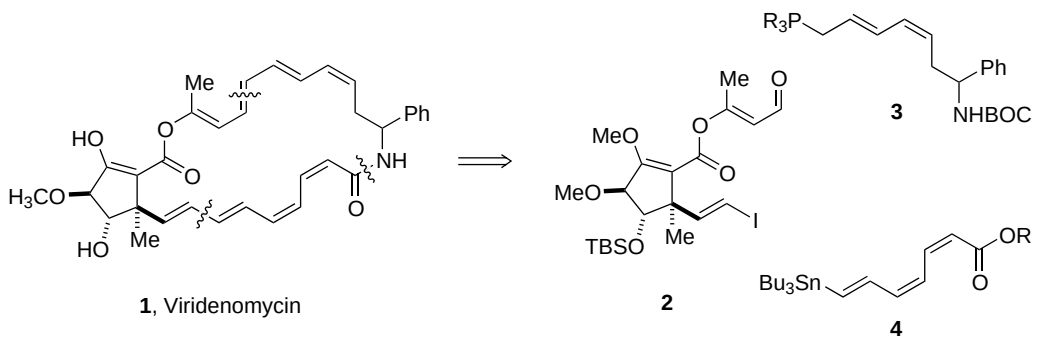
**Abstract**—A second generation approach toward the synthesis of viridenomycin is described. Three key fragments of the molecule have been synthesized in stereochemically pure form. Initial studies toward the coupling of these fragments with the aim of assembling the macrocycle are detailed. Final efforts to reach the title compound are documented. 

In the preceding paper,[1] studies from this laboratory directed toward the total synthesis of viridenomycin **1**, a macrocyclic antibacterial agent,[2] were described. The key components of the latter strategy were: (1) both tetraene constructions via Julia coupling[3] and palladium cross-coupling, followed by alkyne reduction, and (2) macrocyclic closure via amide bond formation. In the course of that work, problems associated with the Julia coupling were identified. We therefore began an alternate strategy for the construction of viridenomycin **1** (Scheme 1). The results are described in this letter.[4]

In order to circumvent the previously encountered problems[1] with the Julia olefination, this new approach includes the use of a phosphorous-based olefination method (i.e. Wittig or Horner–Emmons)[5] to construct the upper tetraene (*E*,*E*,*E*,*Z*) in **1** (Scheme 1). Also concerned by the use of a late-stage alkyne reduction,[1] we opted to attempt direct installation of the lower tetraene (*E*,*E*,*Z*,*Z*) of **1** via a Stille coupling[6] between the vinyl iodide of **2** and the stannyl triene **4**. A lactam bond linkage was envisioned to complete the macrocyclic ring of viridenomycin **1**.

The elaborated cyclopentenyl fragment **2** was prepared via improved modifications of the previously disclosed route (Scheme 2).[7] The point of divergence occurs at allylic alcohol **5**, which was now masked as its benzyl ether **6**. The double bond was dihydroxylated and converted into the corresponding cyclic sulfate **7**,[8] which was regioselectively opened with cesium acetate. The resulting hydroxyl group was protected as a silyl ether and the acetate moiety was hydrolyzed and converted into the required methyl ether **8**. Hydrogenation to remove the benzyl ethers, Swern oxidation of the carbinols,[9] and Takai olefination[10] of the carboxaldehyde produced the key vinyl iodide **9**. Reaction of the enolate of ketone **9** with methylcyanoformate followed




**Scheme 1.**

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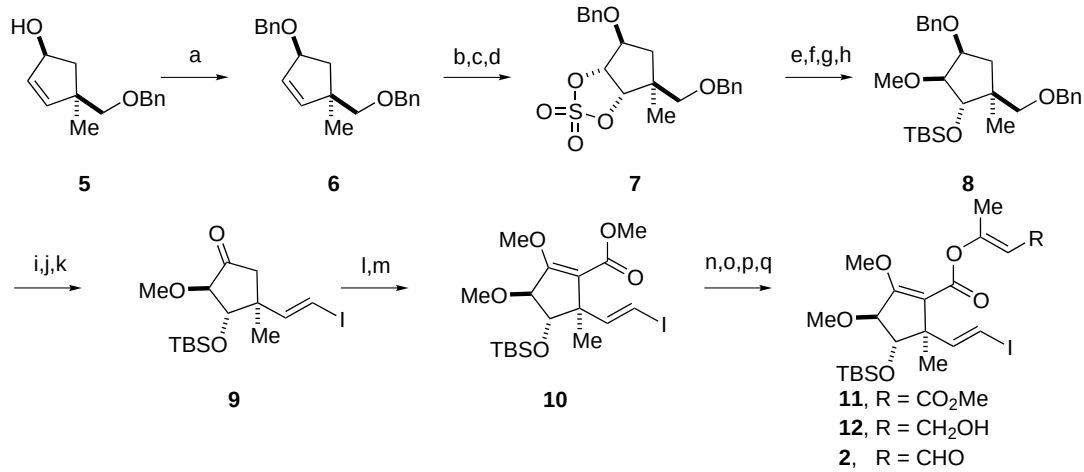



**Scheme 2.** *Conditions*: (a) KH, BnBr, THF, 0°C; (b) $OsO_4$, NMO, acetone/water, −15°C; (c) $SOCl_2$, $Et_3N$, $CH_2Cl_2$, 0°C; (d) $NaIO_4$, $RuCl_3$, $CCl_4/CH_3CN/H_2O$; (e) 1. CsOAc, DMF, 55°C; 2. $H_3O^+$; (f) TBSCl, imidazole, DMF; (g) $K_2CO_3$, MeOH, 55% (seven steps); (h) NaH, MeI, THF; (i) Pd–C, $H_2$, EtOH; (j) DMSO, $Et_3N$, $(COCl)_2$, $CH_2Cl_2$; (k) $CrCl_2$, $CHI_3$, THF, 70% (four steps); (l) LDA, $CNCO_2CH_3$, HMPA, $Et_2O$, −78°C, 64%; (m) $MeO_2SO_2$, DBU, DMSO, 75%; (n) LiOH, dioxane/water, 95°C, 75%; (o) 1. 2,4,6-trichloro-benzoyl chloride, $Et_3N$, THF; 2. methylacetoacetate, $Et_3N$, DMAP, HMPA, 84%; (p) DIBALH, THF, −60°C, 82%; (q) Dess–Martin periodinane, $CH_2Cl_2$, 75%.

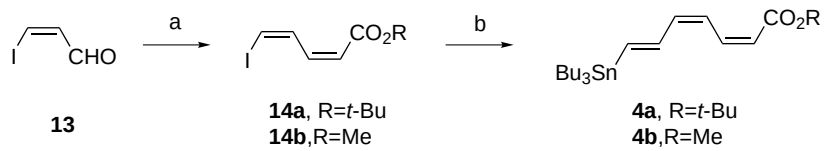
by methylation of the resulting enol gave ester **10**, which was saponified and activated as a mixed anhydride. Condensation of the latter with methyl acetoacetate produced enol ester **11**, while DIBALH reduction to carbinol **12** and Dess–Martin oxidation[11] gave the requisite fragment **2**.

Trienyl fragment **4** was prepared in two variations from known aldehyde **13**[12] (Scheme 3). Use of the appropriate Still–Gennari-style phosphonate[13] afforded the *trans* dienes **14** with greater than 20:1 *E*:*Z* ratios. Palladium coupling with known distannylethylene[14] provided the desired trienes **4**.

The use of phosphonate carbanions to establish the *E* alkene in the linkage of fragments **2** and **3** was our original plan. However, use of a phosphonate (entries a and b, Table 1) resulted in an unfavorable rearrangement in model aldehyde **15**, producing only ketone **16**. We felt that a Wittig reagent, which utilizes a classic ylide, might suppress this rearrangement. Tamura[15] has disclosed that tri-butyl phosphine derived ylides give excellent *trans* olefin ratios when using semistabilized ylides. However, in our hands, reaction of the ylide derived from a tri-butylphosphonium salt (entries c and d) with 2-hexenal **17** gave triene **18** in relatively poor *E*:*Z* ratios. Use of the ylide derived from the deprotonation of a trimethyl phosphine based salt with *n*-BuLi (entry f) gave excellent selectivity, producing triene **19** in a 30:1 ratio, favoring the desired *trans* olefin.[16] Satisfactory results were also obtained using this ylide and the model aldehyde **15** (entry g).

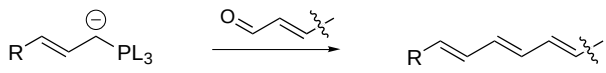
The highly substituted vinyl iodide **2** was next coupled with stannane **4a** in quantitative yield to give tetraene **20** with all of the stereochemical integrity preserved (Scheme 4). Phosphonium salt **21** was prepared from the reaction of trimethyl phosphine and the previously[1] constructed bromide in THF and, due to its hygroscopic nature, was immediately deprotonated with *n*-BuLi to generate the corresponding ylide. Reaction of multiple equivalents of the ylide with aldehyde **20** at −40°C produced the desired bis-tetraene **22** as a 1:1 mixture of olefin isomers, presumably at the newly formed bond. It is interesting to note that the presence of the extended conjugation in aldehyde **20** dramatically reduces the reactivity of the carboxaldehyde group (16–20 h) when compared with model aldehyde **15** (which reacted immediately at −78°C). The slow nature of the reaction may also be responsible for the poor *E*,*Z* selectivity during the Wittig coupling.

With **22**, containing all the requisite atoms of viridenomycin, now in hand, albeit as a mixture of two olefin isomers, attempts to remove both *tert*-butyl based protecting groups in **22** met with abject failure. Various decomposition products were obtained from a variety



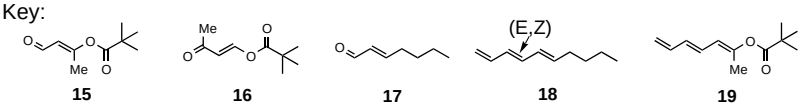

**Scheme 3.** (a) $(CF_3CH_2O)_2POCH_2CO_2R$, KHMDS, 18-Crown-6, THF, −78°C, 78% (**14a**), 91% (**14b**); (b) *trans*-$Bu_3SnCH{=}CHSnBu_3$, $Pd(PPh_3)_4$, THF, 35°C, 61% (**4a**), 58% (**4b**).

**Table 1.** Study of triene construction conditions

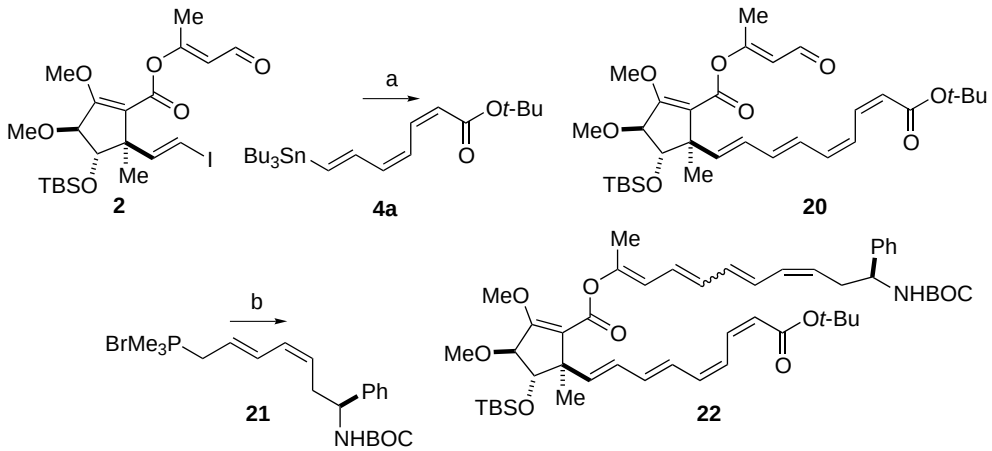


| Entry | R | $PL_3$ | Base | Aldehyde | Product | Ratio (*E*:*Z*) |
|---|---|---|---|---|---|---|
| a | $CH_3$ | $PO(OEt)_2$ | KO*t*-Bu | **15** | **16** | - |
| b | $CH_3$ | $PO(OEt)_2$ | *n*-BuLi | " | " | - |
| c | H | $PBu_3$ | KO*t*-Bu | **17** | **18** | 2.6:1 |
| d | H | $PBu_3$ | *n*-BuLi | " | " | 2.9:1 |
| e | H | $PMe_3$ | KO*t*-Bu | " | " | 3.0:1 |
| f | H | $PMe_3$ | *n*-BuLi | " | " | 30:1 |
| g | H | $PMe_3$ | *n*-BuLi | **15** | **19** | 10:1 (90 %) |

Key:



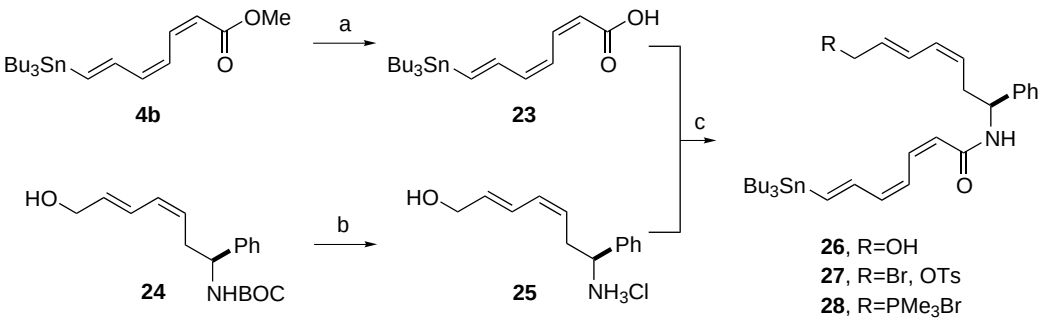
**15** **16** **17** **18** **19**



**2** **4a** **20** **21** **22**

**Scheme 4.** *Conditions*: (a) $PdCl_2(CH_3CN)_2$, DMF, 100%; (b) **21**, *n*-BuLi, THF, then **20**, −40°C, 80%.

of known deprotection conditions. The most common difficulty appeared (NMR) to be acidic hydrolysis of the rather sensitive enol ester bond. Therefore, we felt that the macrocycle might be better constructed via a more convergent strategy, using a moiety such as **28** (Scheme 5), wherein the lactam linkage was already in place. To this end, ester **4b** was saponified and the resulting acid **23** was activated with PyBOP. To this



**4b** **23** **24** **25** **26**, R=OH **27**, R=Br, OTs **28**, R=$PMe_3Br$

**Scheme 5.** *Conditions*: (a) LiOH, *t*-BuOH/water, 95%; (b) HCl, EtOAc, 100%; (c) **23**, EtNi–$Pr_2$, PyBOP, $CH_2Cl_2$, then **25**, 40%.

was added amine salt **25** (prepared from the deprotection of alcohol **24**[1]), resulting in the formation of the B-ring precursor **26** in 40% yield. The lability of the allylic alcohol in **26** appeared to be the primary source of the low conversion, undergoing a number of displacement and/or cyclization side reactions. A variety of attempts to convert the allylic alcohol into the corresponding allylic bromide or tosylate, **27** resulted in the destruction of the molecule. Again, the lability of the allylic hydroxyl and the presence of the vinyl stannane appear to interfere with further attempts to prepare the requisite ylide in this instance (although successful ylide formation was achieved with **21**).

In conclusion, three key pieces involved in a second generation strategy aimed at the total synthesis of viridenomycin have been prepared. In addition, all of the atoms of viridenomycin have been incorporated, however, the final closure of the macrocycle and the completion of the molecule still remains unrealized.[17]

## Acknowledgements

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16. The increase in selectivity is likely due to the decreased size of the methyl ligands on the phosphorous. Thus, this is essentially an enhancement of the effect observed by Tamura (see Ref. 15).
17. Due to personal considerations, the primary author has retired and is no longer in a position to continue this work. However, all spectral data and experimental details for all compounds described herein are on file with the senior author.