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Studies directed toward the synthesis of viridenomycin. Route 1: assembly of three advanced intermediates

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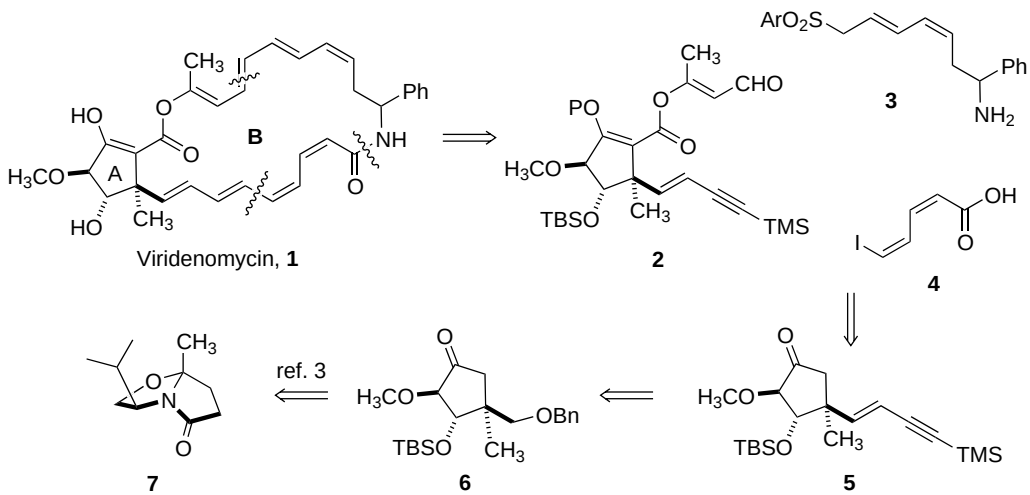
Abstract—Three enantiomerically and geometrically pure building blocks representing fragments of the antifungal antibiotic viridenomycin have been prepared.

Viridenomycin is an antifungal antibiotic that has demonstrated in vivo activity against cancer, prolonging the lifespan of mice with B16 melanoma.[1] The gross structure of **1** contains a highly functionalized cyclopentenyl A-ring and a 24-membered macrocyclic B-ring. The macrocycle is comprised of two tetraene subunits connected by an amide bond linkage. In addition, one of the tetraenes is conjugated to an unstable enol-ester. Our retrosynthetic plan for **1** relies on the convergence of three key fragments **2**–**4** by disconnection of both tetraene subunits and the lactam bond (Scheme 1). The upper tetraene would be installed via a sulfone-based olefination reaction,[2] while the lower tetraene would be assembled by a palladium coupling and late-stage alkyne reduction. Our laboratory recently described[3] the asymmetric assembly of the stereochemically endowed cyclopentenyl A-ring core(**6**) of **1** from the chiral valinol-derived bicyclic lactam **7**.[4] This report will illustrate the further elaboration of the A-ring fragment and our efforts toward reaching the additional fragments necessary for the total synthesis of **1**.

The previously prepared ketone **6**,[3] was hydrogenated with Pd/C to remove the benzyl group and give alcohol **8** (95%). Subsequent oxidation (TPAP/NMO) produced ketoaldehyde **9** in 69% yield (Scheme 2). After olefination[5] to vinyl iodide **10** using $CrCl_2$ and CHI_3 (69%), coupling[6] with trimethylsilyl-acetylene in the presence of $PdCl_2(CH_3CN)_2$ gave eneyne **11** (57%). Acylation[7] of the enolate derived from cyclopentanone



Scheme 1.

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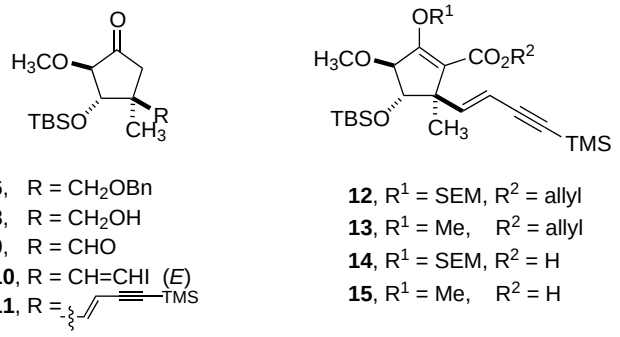
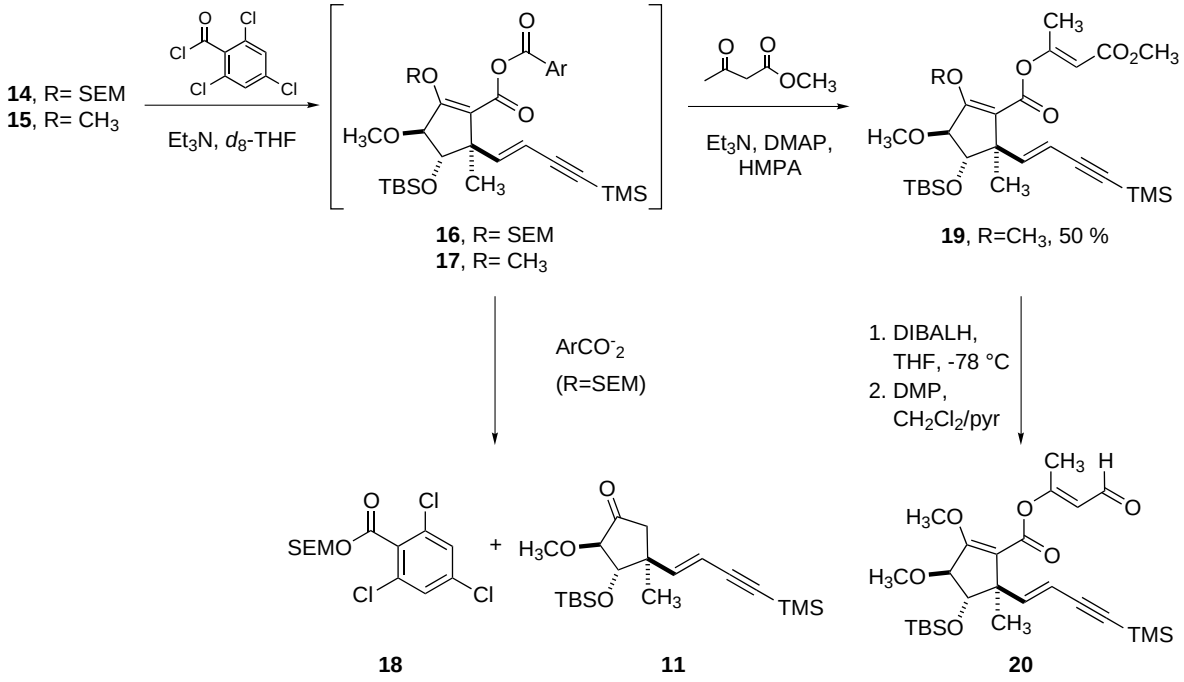


6, R = CH_2OBn
8, R = CH_2OH
9, R = CHO
10, R = CH=CHI (*E*)
11, R = TMS

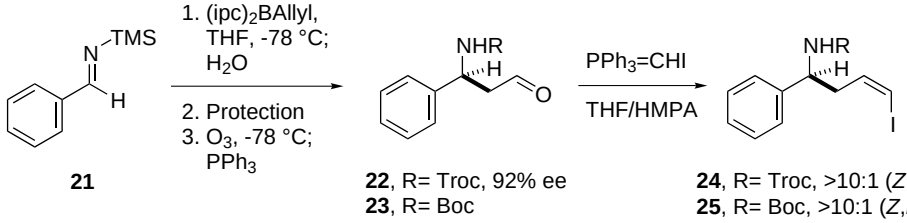
12, R^1 = SEM, R^2 = allyl
13, R^1 = Me, R^2 = allyl
14, R^1 = SEM, R^2 = H
15, R^1 = Me, R^2 = H

Scheme 2.

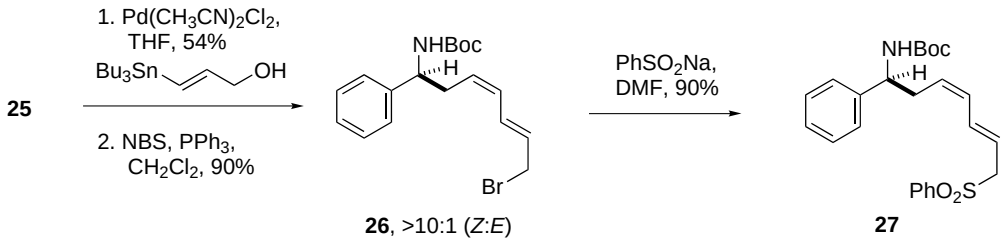
11 with allylcyanoformate was very sensitive to reaction conditions and, therefore, the best yield obtained in THF was only ca. 40%.[3] However, when ether was used as the solvent and 1 equiv of HMPA was employed, ester **12** was obtained in 76% yield after installing the SEM group. Removal of the allyl ester under Pd(0) catalysis gave the requisite carboxylic acid **14**, required for affixing the enol-ester in **2**. The next step was to generate a mixed anhydride[8] and treat this with the enolate of methyl acetoacetate to form an enolester (e.g. **19**) with a high degree of stereocontrol.[9] On addition of 2,4,6-trichlorobenzoyl chloride to **14** (Scheme 3), anhydride **16** was observed by ^1H NMR (d_8-THF). However, the anhydride was observed to quickly decompose to the SEM protected trichlorobenzoate **18** and the parent ketone **11**. A plausible explanation for the instability of anhydride **16** involves nucleophilic attack on the methylene group of the SEM group by $ArCO_2^-$, presumably leading to the formation of an intermediate α-keto ketene, which, after hydrolysis and decarboxylation, would lead to the formation of the observed ketone **11**. With the SEM group implicated in the decomposition of anhydride **16**, the more stable *O*-methyl group replaced the SEM group, leading ultimately to the formation of the *O*-methoxy acid **15** (Scheme 2). This was accomplished by treatment of the enol resulting from acylation of **11** with diazomethane, to give the methyl enol ether **13** (72%). Conversion, as before, to acid **15**, followed by activation using 2,4,6-trichlorobenzoyl chloride afforded the methoxy substituted anhydride **17**, which proved to be stable by ^1H NMR (Scheme 3). The latter was immediately transformed, as above, to the enol-ester **19** (50%). The carbomethoxy group of **19** was reduced to the corresponding allylic alcohol with DIBALH and then oxidized to enal **20** with the Dess–Martin reagent[10] to complete the synthesis of a protected version of the requisite fragment **2** shown in Scheme 1.



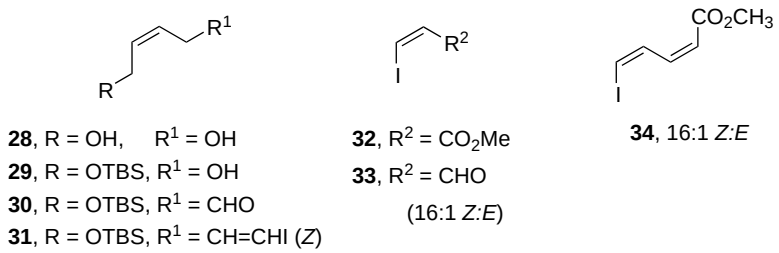
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

The synthesis of fragment **3** was initiated by allylation of imine **21** at −78°C using (+)-$(ipc)_2$B-allyl (Scheme 4).[11] Protection of the amine as the Troc-carbamate, followed by ozonolysis, produced the aldehyde **22** in 92% ee and 75% yield. Wittig homologation[12] gave **24** in greater than >10:1 (*Z*:*E*) ratio, but in low chemical yield (ca. 40%). However, utilization of the corresponding Boc-derivative **23**[13] increased the chemical yield of vinyl iodide **25** to 73%, with a >10:1 ratio of *Z*:*E* olefins.

Palladium-catalyzed coupling of the vinyl iodide **25** with the known vinylstannane[14] gave the (*Z*,*E*)-dienylalcohol, which was directly converted into the somewhat labile bromide **26** (Scheme 5). Displacement of the bromide with sodium phenyl sulfinate in DMF produced the allylic sulfone **27**, corresponding to the requisite fragment **3**.

The (*Z*,*Z*)-dienyl iodide **4** (Scheme 1) was initially found to be difficult to reach in greater than ~8:1 (*Z*:*E*) stereoselectivity. An early approach utilized mono-silylation of the readily available *cis*-butene-diol **28** to the *t*-butyldimethylsilylether **29** and subsequent oxidation of the remaining allylic alcohol with Dess–Martin periodinane[10] to afford enal **30** (Scheme 6). The latter was thermally unstable to *E*/*Z* isomerization and had to be elaborated immediately. Unfortunately, olefination[12] produced diene **31** in only a modest 7.5:1 ratio of (*Z*) to (*E*) isomers at the newly formed double bond. Unable to separate the isomers, this route was abandoned in favor of the following. Methyl (*Z*)-iodoacrylate **32** (>99:1, *Z*/*E*)[15] was reduced using DIBALH to afford the (*Z*)-iodo-acrolein **33**, which now exhibited less erosion of the alkene stereochemistry (16:1, *Z*/*E*).[15] Application of a modification[16] of the Horner–Wadsworth–Emmons reaction furnished the iododienoate **34** as an acceptable 16:1 mixture of isomers. Hydrolysis (LiOH) of the ester of **34** led to fragment **4** required for the route to viridenomycin.

In summary, the three key fragments (**2**–**4**) required for the total synthesis of **1** have been prepared. Unfortunately, the Julia coupling[2] required to join fragments **2** and **4** failed to produce consistent alkene formation in a closely related model system and thus discouraged further efforts dedicated to this route. An alternate plan, with new synthetic strategy was next embarked on.[17]

Acknowledgements

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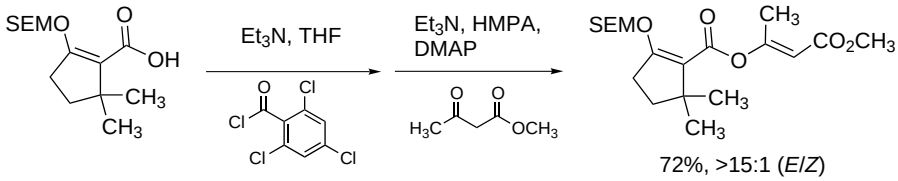

72%, >15:1 (*E*/*Z*)

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