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# Asymmetric synthesis of the core cyclopentane of viridenomycin

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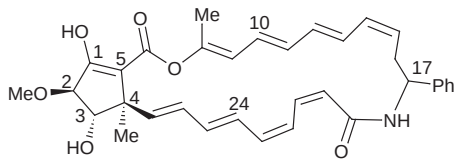
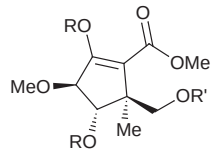
**The fully substituted cyclopentene ring with three stereogenic centers has been efficiently constructed for the first time using chiral bicyclic lactams, the insertion of the quaternary center being the key step; ring opening of chiral sulfates to the correct 1,2-dihydroxy substituents also played a major role in reaching 1 in suitable form (18) for further study.**

Recently, a natural product was isolated from the culture broth of an actinomycete identified as *Streptomyces gannmycicus*, and upon structure determination, it was found that this compound was identical to viridenomycin, a natural product that had been known for some time, but which had not been structurally characterized.[1] Viridenomycin has been shown to




Viridenomycin




**1**

act as an antifungal antibiotic, and additionally has prolonged the survival of mice infected with B16 melanoma. It is structurally very similar to the natural product hitachimycin,[2,3] although viridenomycin has not yet been the subject of any reported synthetic efforts. It has, as its core, a highly functionalized cyclopentene ring **1** with three contiguous stereogenic centers, one of which is quaternary. Additionally, the absolute stereochemistry of viridenomycin is still unknown with the stereochemistry at C-17 still in question.

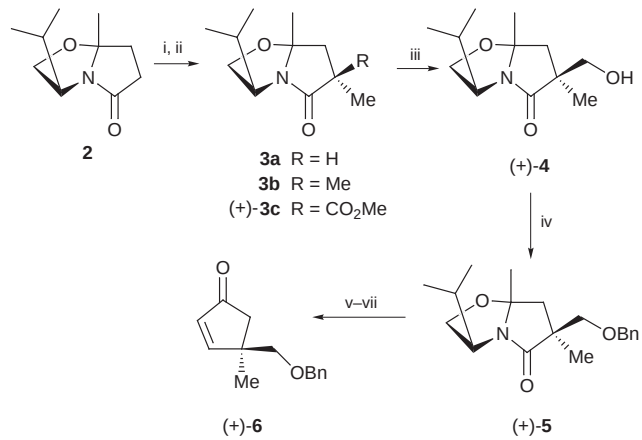
With our interest in chiral, bicyclic lactams as templates for a variety of enantiomerically pure compounds containing quaternary stereocenters, the C-4 position of viridenomycin suggested the possibility of an asymmetric synthesis.

The requisite chiral bicyclic lactam **2** (Scheme 1) was readily prepared by condensation of levulinic acid and enantiomerically pure natural valinol.[4] Treatment of **2** with LDA followed by MeI quench gave a mixture of products, containing primarily the desired α-methyl bicyclic lactam **3a**, in addition to some of the α,α-dimethylated compound **3b**.[5] The latter was only partially separable from the desired compound, so the crude product was simply carried on and directly treated again with LDA. The resulting enolate was quenched with $ClCO_2Me$, giving **3c** with high (> 98%) diastereoselectivity (NMR). Again, the α,α-dimethylated derivative **3b** was difficult to remove, and the mixture of **3b** and **3c** was carried forward. It had been previously observed[6] that acylating agents such as acid chlorides approached the lactam enolate in an *exo* fashion, so an *exo* approach to **3c** was hypothesized for the present transformation. The stereochemistry would be confirmed at a later time.

Reduction of the quaternary lactam ester **3c** with $NaBH_4$ in EtOH furnished the corresponding alcohol **4**, in high overall yield (65%) for the first three steps (**2**–**4**). The alcohol **4** was now easily separable from the accompanying α,α-dimethyl material **3b**. An X-ray crystal structure of alcohol **4** was obtained and confirmed that the hydroxymethyl group in **4** was indeed on the β-face of the molecule. This is the first published example of the lactam enolate of **2** acylating preferentially from the *exo* face. The hydroxymethyl side chain of **4** was transformed to its benzyl ether **5** in 96% yield, and the chiral auxiliary removed by reduction–hydrolysis to yield the cyclopentenone **6** with high efficiency (76%) for the three step process (**5** → **6**).

Studies were undertaken to access the allylic alcohol **7a**, *via* various reducing agents in anticipation of subsequent olefin dihydroxylation, to **9**. Since the benzyl protected hydroxymethyl side chain may be considered larger than the methyl group in **6**, it was expected that reducing agents should approach preferentially from the bottom face of the cyclopentenone **6**, to yield the β-OH group. It was found (Scheme 2) that the highest stereoselectivity could be realized (3.5 : 1) utilizing DIBAL-H[7] to afford **7a**. This modest selectivity was considered acceptable because the major isomer **7a** could be isolated in good (78%) yield, and the undesired α-OH isomer **7b** was also recyclable by oxidizing to the enone **6** with $CrO_3$ in high (86%) yield.

Repetitive reductions with DIBAL-H produced additional quantities of **7a**. The latter was converted to its *p*-methoxybenzyl (PMB) ether **8**, (KH, PMBCl) in 95% yield. Osmylation proceeded smoothly (90%) to give an inseparable mixture of diastereomeric diols **9** with relatively high (10 : 1) selectivity. The protons at C-2, C-3 (viridenomycin numbering) in **9** were sufficiently discernible in the NMR to determine the level of selectivity. Cyclic sulfate formation was accomplished using the Sharpless technique,[8,9] producing a single isomer (**10**) in




**2**

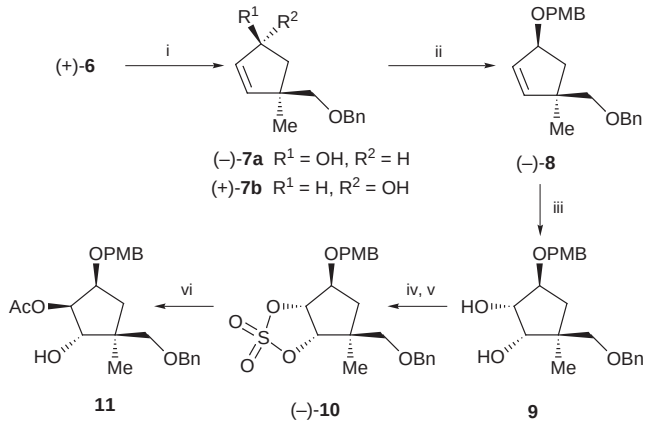
**3a** R = H
**3b** R = Me
(+)-**3c** R = $CO_2Me$

(+)-**4**

(+)-**6**

(+)-**5**

**Scheme 1** *Reagents and conditions*: i, LDA, MeI, THF, −78 °C → rt; ii, LDA, $ClCO_2Me$, THF, −78 °C → rt (50 : 1 dr); iii, $NaBH_4$ (7 equiv.), EtOH, 0 °C → rt (65%, 3 steps); iv, NaH, BnCl, DMF, 0 °C → rt (95%); v, Red-Al (6.6 equiv.), THF, −25 °C, 2 d; vi, $NBu_4NH_2PO_4$ (50 equiv.), EtOH–$H_2O$ (1 : 1); vii, KOH (0.1 equiv.), THF (76%, 3 steps).

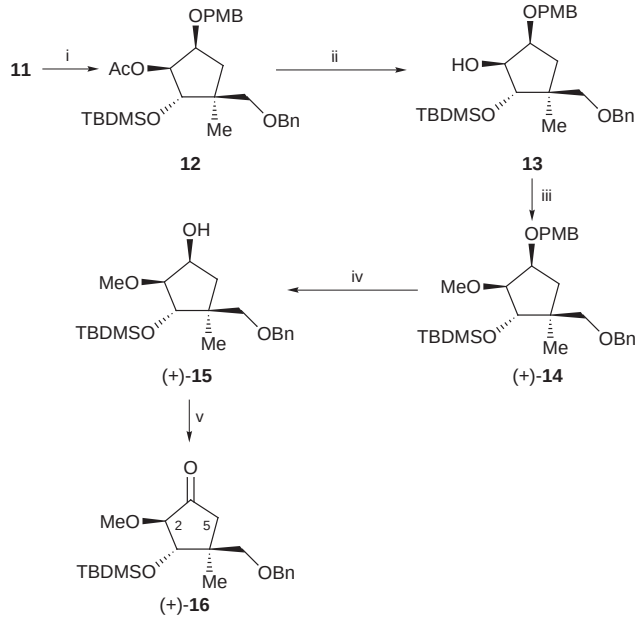


**Scheme 2** *Reagents and conditions*: i, DIBAL-H (1.5 equiv.), THF. −78 °C (99%, 3.5:1 dr); ii, KH, (2.2 equiv.) PMBCl, DMF, 0 °C (95%); iii, $K_2OsO_2{\cdot}H_2O$, NMO, acetone–$H_2O$ (3:1) (90%, 10:1 dr); iv, $SOCl_2$, $Et_3N$, $CH_2Cl_2$, 0 °C; v, $RuCl_3{\cdot}H_2O$, $NaIO_4$, $CCl_4$–$H_2O$–MeCN (1:1.4:1) (85%, 2 steps); vi, CsOAc (5 equiv.), DMF, 40 °C, then $H_2SO_4$, THF (99%, 9:1 dr).

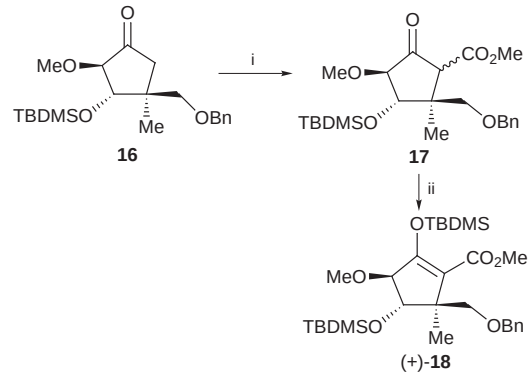
satisfactory (77%) yield for the two steps. Caesium acetate opening of the sulfate **10** occurred with high regioselectivity (10:1) and yield (99%) to furnish the acetoxy alcohol **11** as the major regioisomer. In this case, the regioisomeric products were not separable and thus the mixture was carried forward.

Protection of the alcohol **11** (Scheme 3) was accomplished in excellent yield (96%) with TBDMSCl and imidazole affording the acetate **12** which was removed by $K_2CO_3$ in MeOH to give a quantitative crude yield of **13**. Methyl ether formation was accomplished on crude **13** in the usual manner to furnish methoxy derivative **14**. At this stage the regioisomeric impurity in **11** obtained by opening the cyclic sulfate was found to be separable and the slightly lower yield of this step (86%) reflects the removal of the undesired isomer.

It was now necessary to remove the PMB ether in **14**. Oxidative cleavage with CAN resulted in several products, thus



**Scheme 3** *Reagents and conditions*: i, TBDMSCl, imidazole, DMAP (91%); ii, $K_2CO_3$, MeOH (100%); iii, NaH (2.5 equiv.), MeI, 0 °C (86%); iv, DDQ (1.3 equiv.), $CH_2Cl_2$–$H_2O$ (5:1) (93%); v, $(COCl)_2$, DMSO, $Et_3N$, −78 °C (91%).



**Scheme 4** *Reagents and conditions*: i, LDA, HMPA (25 equiv.), $NCCO_2Me$, −78 → −20 °C; ii, TBDNCl, imidazole, DMAP (40%, 2 steps).

the cleavage was performed with DDQ, which quickly removed the PMB group in good yield (93%) and gave the free C-1 alcohol **15**. Mild oxidation under Swern conditions produced the desired ketone **16** (91%).

The enolate of **16** was generated in the presence of HMPA[10] as cosolvent and warmed to −40°C before quenching with $NCO_2Me$. Enolate formation generated small amounts of the epimerized **16** and elimination products. However, the desired product **17** was the major constituent of the mixture, along with still significant quantities of undesired products. It appears from all of these experiments that the source of epimerization was not initial generation of the incorrect enolate, but was due to facile proton transfer processes after the addition of the electrophile.

Having obtained a quantity of the carboxylated derivative, **17**, attention was turned to isolation of the enol ester **18**, the intended target of this study (Scheme 4). Attempts to silylate **17** gave an enol ether, which was poorly characterized. By combining the two steps from **16** to **18** (no attempt was made to purify the β-keto ester **17**), the crude material was directly silylated and gave an overall yield of **18** of 40%. With the acquisition of **18**, all of the correct regio- and stereo-chemical features have been installed and the substituents at the 4- and 5-positions are in a position to further extend the synthesis to viridenomycin itself.

Further studies are in progress to introduce into **18** the 24-membered polyene ring of viridenomycin.

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## Notes and references


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