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A route to the fully substituted cyclopentane unit of viridenomycin using a tandem radical cyclisation–trapping strategy

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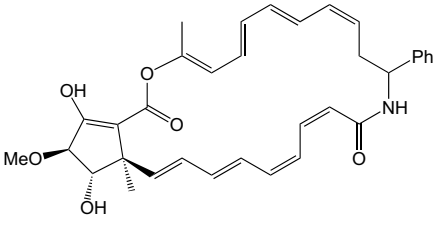
Abstract—A silicon-tethered intramolecular radical cyclisation, in tandem with a radical trapping with allyltri-*n*-butylstannane forms the basis of a new synthetic strategy to the cyclopentane core of the antitumoral antibiotic substance viridenomycin isolated from *Streptomyces viridochromogenes* and *S. gannmycicus*.

Viridenomycin **1** is an antitumoral antibiotic substance isolated from *S. viridochromogenes* and *S. gannmycicus*[1] which is capable of prolonging the life span of transgenic mice who express P388 leukaemia and B16 melanoma. The compound has a structure based on a polyene macrolactam core linked to a highly substituted cyclopentane, viz **2**, by a quaternary centre and via an enolised β-keto ester unit. Although neither the absolute stereochemistry nor the stereochemistry at the benzylic centre in viridenomycin is known, the striking structural features it accommodates, alongside its interesting biological properties, have combined to make the natural product a challenging target for synthesis.



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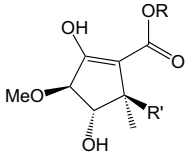

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Arrington and Meyers[2] were the first to describe a concise synthesis of the cyclopentane core in viridenomycin and more recently Ishihara et al.[3] and Trost and Jiang[4] presented alternative solutions to this demanding synthetic problem. In this paper we describe a different synthetic approach to the cyclopentane ring system in viridenomycin which uses an intramolecular radical cyclisation from a silicon tethered 2-cyclopentenol, that is, **3**, in tandem with in situ trapping of the product radical with allyltri-*n*-butylstannane, leading to **4**, as the key stratagem (Scheme 1).[5]

Thus, the known substituted tetrahydrofuran **6** derived from commercially available 1,2-5,6-di-*O*-isopropylidene-α-D-glucofuranose[6] **5** was first converted into the corresponding γ-lactone **7** in four straightforward steps (Scheme 2). Addition of methyllithium to **7**, followed by protection of the resulting γ-hydroxyketone **8a** next led to the methyl ketone **8b**, which was then converted into the corresponding alkene **9** using the Nysted reagent ($(Zn(CH_2ZnBr)_2 \cdot THF–TiCl_4)$).[7] The 1,6-diene **9** underwent smooth ring closure metathesis in the presence of Grubbs' catalyst[8] at 80 °C to give the cyclopentene **10** in 90% yield.

Deprotection of the silyl ether **10**, followed by treatment of the resulting cyclopentenol with (bromomethyl)chlorodimethylsilane in the presence of DMAP and Et_3N then gave the key α-bromosilyl ether **11** in 80% yield (Scheme 3). To our satisfaction, when a solution of the α-bromosilyl ether **11**, allyltri-*n*-butylstannane and

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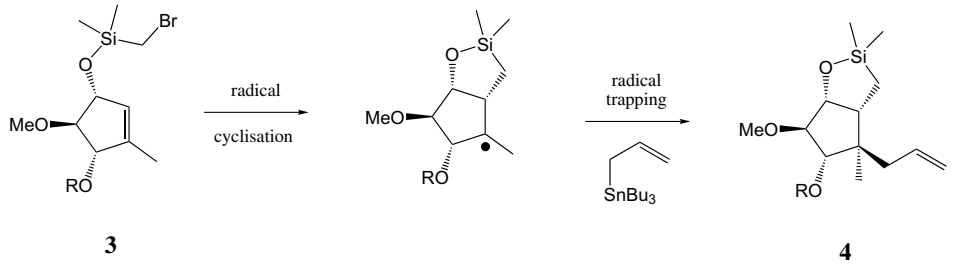
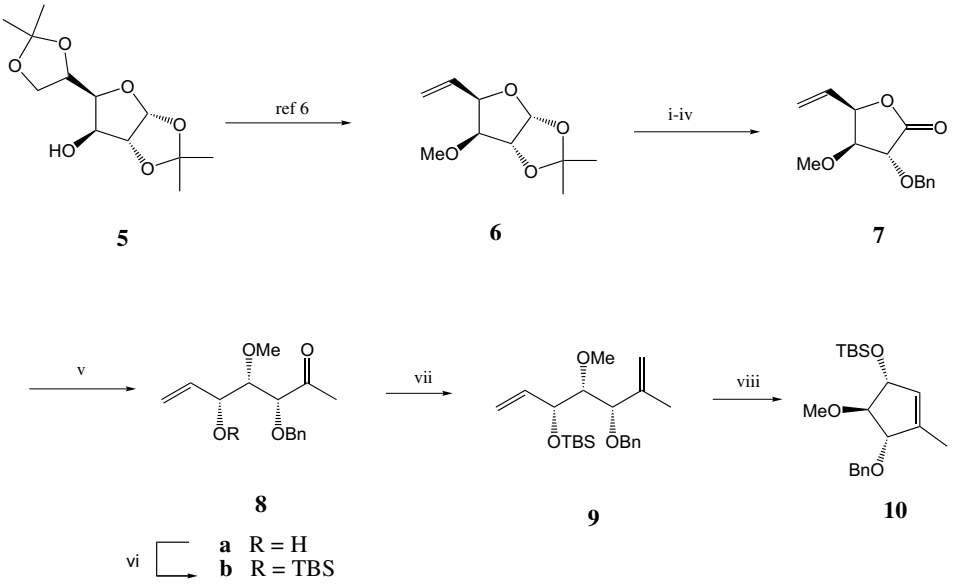


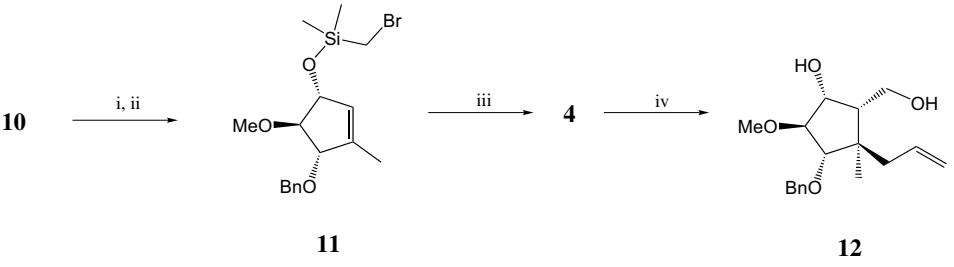
3 4

Scheme 1.



5 6 7 8 9 10

Scheme 2. Reagents and conditions: (i) EtOH, HCl in dioxane, 60 °C (91%); (ii) BnBr, NaH, DMF, 0 °C (89%); (iii) AcOH, H_2O (98%); (iv) DMSO, Ac_2O (91%); (v) MeLi, THF, −78 °C; (vi) TBSCl, imidazole, DMF (54%); (vii) $Zn(CH_2ZnBr)_2{\cdot}THF$, $TiCl_4$, THF, 0 °C–rt (98%); (viii) 1,3-(bis(mesityl)-2-imidazolidinylidene)dichloro-(phenylmethylene)(tricyclohexylphosphine)ruthenium, benzene, 80 °C (90%).

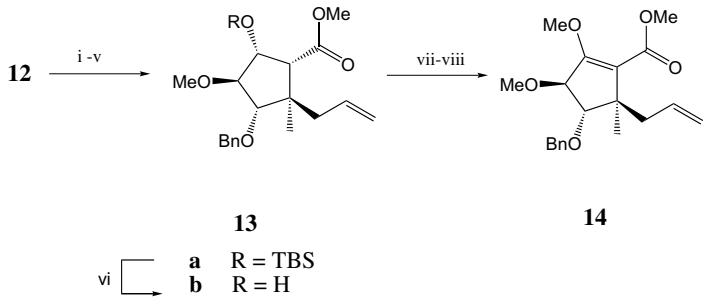


11 12

Scheme 3. Reagents and conditions: (i) TBAF, THF (80%); (ii) Et_3N, $(CH_3)_2Si(CH_2Br)Cl$, DMAP, DCM (80%); (iii) ACCN, *n*-heptane, 100 °C, allyltri-*n*-butylstannane; (iv) H_2O_2, KF, $KHCO_3$, MeOH, THF, 80 °C (50% over two steps).

1,1′-azobis(cyclohexanecarbonitrile) (ACCN) in *n*-heptane, was heated at 100 °C for 24 h, work-up gave the silicon heterocycle (**4**, R = Bn) which was immediately treated with H_2O_2–KF in THF–MeOH under reflux, that is, Tamao–Fleming oxidation conditions,[9] to give the cyclopentane-substituted diol **12** containing five contiguous chiral centres, in 50% overall yield. The stereochemistry of **12** followed unambiguously from NOE studies. Thus irradiation of the quaternary methyl group at δ 1.1 in **12**, gave enhancements at δ 3.9 and δ 3.8 due to the CH_2OH protons (5.1 and 5.3%, respectively), and irradiation at δ 4.3 (C$H{\cdot}CH_2$OH) resulted in enhancements at δ 3.8 (CH_2OH; 4.8%) and δ 2.2 (CH_2CH:CH_2; 20.1%).

The primary alcohol group in **12** was next converted into the corresponding carboxylic acid ester **13a** in straightforward steps, which was then deprotected to the secondary alcohol **13b** (Scheme 4). Oxidation of **13b** using Moffatt conditions,[10] followed by methylation of the enol of the resulting β-keto ester, finally gave the cyclopentane unit **14** of viridenomycin, appropriately



Scheme 4. Reagents and conditions: (i) TBSCl, imidazole, DMF (92%); (ii) PPTS, EtOH (71%, based on recovered starting material); (iii) DMP, pyridine, DCM; (iv) $NaClO_2$, KH_2PO_4, H_2O, *t*-BuOH, 2-methyl-2-butene; (v) $TMSCHN_2$, PhH, MeOH; (vi) TBAF, THF (69%, over four steps); (vii) EDC, DMSO, Py·TFA, DMAP (89%); (viii) Me_2SO_4, DMSO, K_2CO_3 (97%).

functionalised for elaboration to the natural product. These and other studies with highly functionalised 5-ring carbocycles, are now underway in our laboratory.

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