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A Novel, Efficient, Diastereo- and Enantioselective Mukaiyama Aldol-Based Synthesis of a Vinyl Cyclopentanone Core Derivative of Viridenomycin

Andrei S. Batsanov,[†] Jonathan P. Knowles,[†] Andrew P. Lightfoot,[‡] Graham Maw,[§] Carl E. Thirsk,[†] Steven J. R. Twiddle,[†] and Andrew Whiting*,[†]

Department of Chemistry, Durham University, Science Laboratories, South Road, Durham DH1 3LE, U.K., GlaxoSmithKline Pharmaceuticals, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, U.K., and Pfizer Global Research & Development, Sandwich, Kent CT13 9NJ, U.K.

andy.whiting@durham.ac.uk

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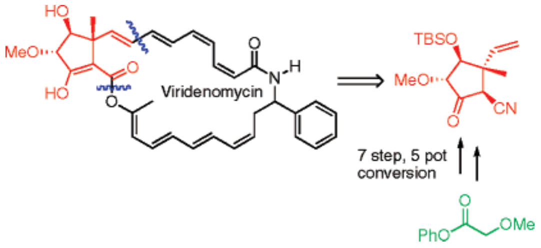
ABSTRACT



A strategy has been developed for a rapid seven-step construction of a chiral, nonracemic vinyl cyclopentanone building block as part of a synthetic approach to viridenomycin, using a diastereo- and enantioselective Mukaiyama aldol and intramolecular Knoevenagel condensation as key steps.

Polyene macrolide viridenomycin **1** was first isolated from a culture broth of *Streptomyces viridochromogenes*[1] and was shown to have antibiotic and antitumor activity.[2] Although the relative stereochemistry of the cyclopentanone ring has been assigned, the absolute stereochemistry of both this five-ring section and the remote α-amide chiral center remains unknown.[3]

Viridenomycin **1** shares many similarities with hitachimycin whose absolute stereochemistry has been assigned.[4] Despite the efforts of several groups[5] and ourselves,[6] viridenomycin **1** has yet to succumb to total synthesis. Several routes to the highly functionalized cyclopentanone core have recently been published,[5a−d] and in this contribution, we report a concise asymmetric and highly diastereoselective assembly of a cyclopentenone derivatives related to **4** and their Michael additions to access derivatives of **2** ready for elaboration to viridenomycin **1**.

[†] Durham University.

[‡] GlaxoSmithKline Pharmaceuticals.

[§] Pfizer Global Research & Development.

(1) Hasegawa, T.; Kamiya, T.; Henmi, T.; Iwasaki, H.; Yamatodani, S. *J. Antibiot.* **1975**, *28*, 167−175.

(2) Nakagawa, M.; Toda, Y.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Antibiot.* **1992**, *45*, 1133−1138.

(3) Nakagawa, M.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1991**, *32*, 659−662.

(4) Smith, A. B. *Pure Appl. Chem.* **1989**, *61*, 405−408.

(5) (a) Trost, B. M.; Jiang, C. *Org. Lett.* **2003**, *5*, 1563−1565. (b) Mulholland, N. P.; Pattenden, G. *Tetrahedron Lett.* **2005**, *46*, 937−939. (c) Pattenden, G.; Blake, A. J.; Constandinos, L. *Tetrahedron Lett.* **2005**, *46*, 1913−1915. (d) Arrington, M. P.; Meyers, A. I. *Chem. Commun.* **1999**, 1371−1372. (e) Kruger, A. W.; Meyers, A. I. *Tetrahedron Lett.* **2001**, *42*, 4301−4304. (f) Waterson, A. G.; Kruger, A. W.; Meyers, A. I. *Tetrahedron Lett.* **2001**, *42*, 4305−4308. (g) Ishihara, J.; Hagihara, K.; Chiba, H.; Ito, K.; Yanigasawa, Y.; Totani, K.; Tadano, K. *Tetrahedron Lett.* **2000**, *41*, 1771−1774.

(6) (a) Batsanov, A. S.; Knowles, J. P.; Whiting, A. *J. Org. Chem.* **2007**, *72*, 2525−2532. (b) Maw, G. N.; Thirsk, C. E.; Toujas, J.-L.; Vaultier, M.; Whiting, A. *Synlett* **2004**, *7*, 1183−1186.

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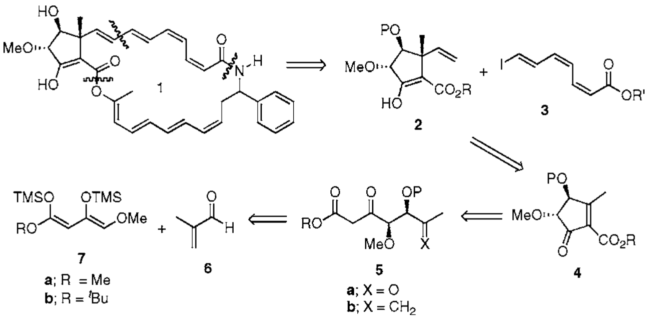
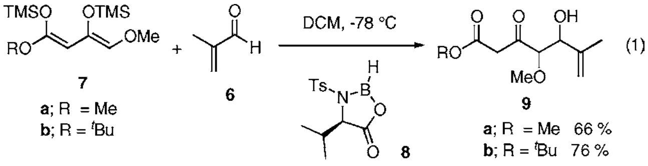
Scheme 1. Retrosynthetic Analysis of Viridenomycin **1**



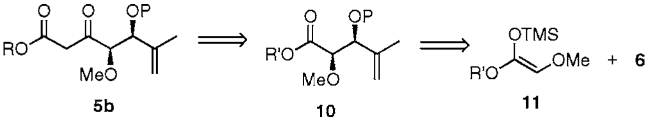
Our initial retrosynthetic analysis of viridenomycin **1** assumes the absolute stereochemistry as drawn in Scheme 1 and involves a potential Heck−Mizoroki coupling of **2** and **3** to assemble the northern hemisphere. In turn, cyclopentanone **2** could be assembled via a stereoselective Michael addition onto cyclopentenone **4**, which could be further disconnected through an intramolecular Knoevenagel condensation of methylketone **5a**. The ketone **5a** could be obtained from oxidative cleavage of alkene **5b**, potentially available from a diastereo- and enantiocontrolled aldol addition of a diene of type **7** (such as Brassard's diene **7a**[7]) to methacrolein **6**. Although asymmetric catalytic aldol reactions of trimethylsilylketene acetals are well-known,[8] the application of such processes to dienolate equivalents might be expected to follow *syn*-selectivity on the basis of established models using asymmetric oxazaborolidinone Lewis acid catalysis.[9]

Thus reactions of Brassard's diene **7a** and the corresponding *tert*-butyl system **7b**,[10] using an oxazaborolidinone-catalyzed Mukaiyama aldol[9] with methacrolein **6**, were found to proceed smoothly, furnishing the desired adducts **9a** and **9b** in 66 and 76% yields, respectively (eq 1). However, attempts at categorically determining the level of diastereo- or enantioselectivity of systems **9** met with failure; these compounds exist as a complex mixture of keto−enol tautomers, which makes structural analysis difficult. Indeed, attempts at derivatization and analysis were similarly unrewarding.



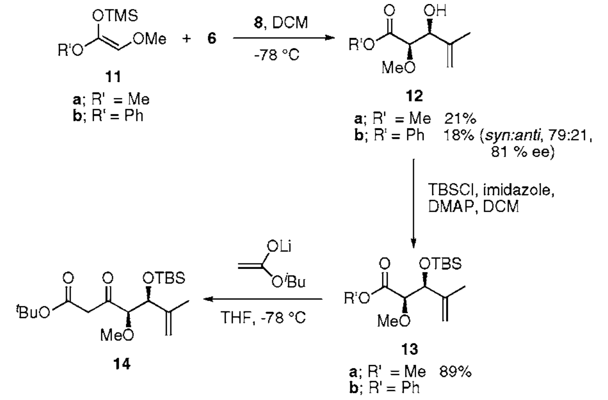
Our inability to determine both relative and absolute stereocontrol in the aldol addition of dienolate equivalents **7** led us to slightly revise our retrosynthetic analysis employing a potentially more readily scrutinized aldol adduct (i.e., **10**), which could undergo a Claisen ester reaction to give a system of type **5b** (Scheme 2).

Scheme 2. Revised Retrosynthetic Analysis of β-Keto Ester **5a**



Hence, TMS ketene acetal **11a**[11] (Scheme 3) was exposed to oxazaborolidinone **8** promoted Mukaiyama aldol reaction.[9]

Scheme 3. Initial Examination of an Aldol−Claisen Sequence to **5**



However, this resulted in disappointing results: stoichiometric **8** being required and providing only 21% yield of aldol adduct **12a** with poor diastereoselectivity (*syn*:*anti*, 3:2). It was also found that, after alcohol protection to give **13a**, the subsequent Claisen ester reaction to give **14** would not proceed on the methyl ester. We, therefore, aimed to access the more reactive phenol ester analogue **13b** by an analogous route (Scheme 3) with the expectation that the better leaving group would enable the Claisen ester conversion (i.e., **13b** to **14**). Thus, ketene acetal **11b** was prepared in two steps from methoxyacetyl chloride.[12]

Initial attempts at this reaction using literature methods based on tin(II) triflate and chiral diamine[13] gave poor yields and racemic product. Better results were obtained when oxazaborolidinone **8** was employed, whereupon phenol ester **12b** was obtained in 81% ee, albeit in low yield (Scheme

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[7] Simoneau, B.; Brassard, P. *Tetrahedron* **1986**, *42*, 3767−3774.

[8] For a review, see: Nelson, S. G. *Tetrahedron: Asymmetry* **1998**, *9*, 357−389.

[9] (a) Yokohawa, F.; Sameshima, H.; Shioiri, T. *Tetrahedron Lett.* **2001**, *42*, 4171−4174. (b) Kiyooka, S.; Hena, M. A. *J. Org. Chem.* **1999**, *64*, 5511−5523. (c) Kiyooka, S.; Hena, M. A.; Goto, F. *Tetrahedron: Asymmetry* **1999**, *10*, 2871−2879.

[10] Diene **7b** was prepared from methyl methoxyacetate using a Claisen ester and double deprotonation−silylation sequences (see Supporting Information).

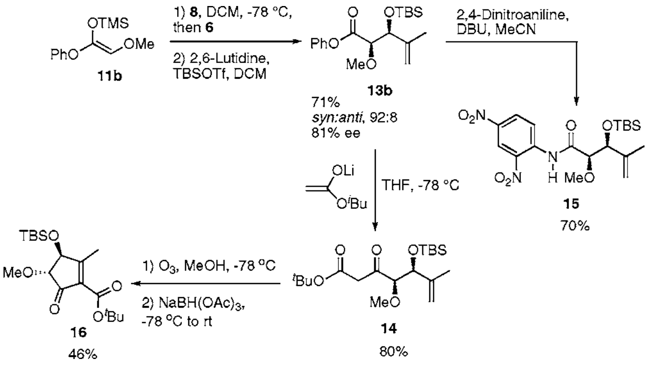
[11] Wissner, A. *J. Org. Chem.* **1979**, *44*, 4617−4622.

[12] Commercially available methoxyacetyl chloride was converted to the phenyl methoxyacetate, followed by conversion to the TMS-ketene acetal (see Supporting Information).

[13] (a) Kobayashi, S.; Hayashi, T. *J. Org. Chem.* **1995**, *60*, 1098−1099. (b) Kobayashi, S.; Uchiro, H.; Shina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761−1772.

3), and stoichiometric amounts of the oxazaborolidinone **8** were required. The low yields of the aldol reaction, together with the moderate diastereoselectivity, led us to optimize the aldol reaction to give **12b** and subsequent secondary alcohol protection and Claisen ester condensation to access **14**, the results of which are outlined in Scheme 4.

Scheme 4. Diastereo- and Enantioselective Synthesis of Cyclopentenone **16**



By employing an alternative desilylation method[14] after the aldol reaction of **11b** and reprotection of the alcohol (**12b**) without actual isolation, the TBDMS ether **13b** was isolated in 71% yield and 81% ee. Importantly, good diastereoselectivity was also found, and the two diastereoisomers could be separated by chromatography giving a *syn*:*anti* ratio of 92:8 (Scheme 4). Attempts to obtain a single-crystal X-ray structure proved unsuccessful; however, reaction of the phenol ester with 2,4-dinitroaniline and DBU provided crystalline amide **15**, which was amenable to X-ray analysis.[15] The absolute stereochemistry was as we had envisaged (see Figure 1) based upon literature models for oxazaborolidinone-mediated Mukaiyama aldol reactions.[9]

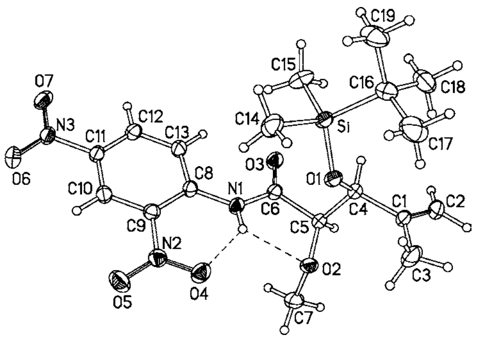
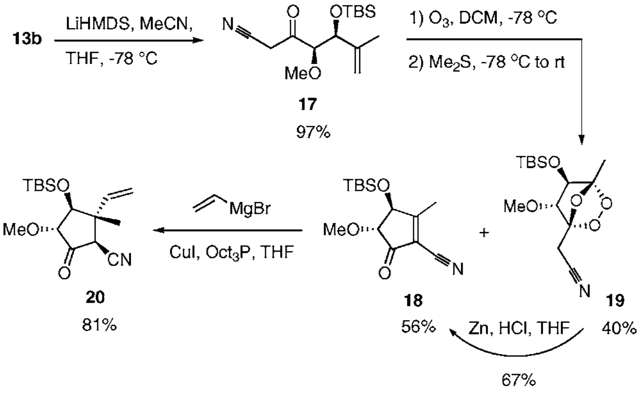


Figure 1. X-ray structure of amide **15** (50% thermal ellipsoids).

Having ascertained that both the correct relative and predicted absolute configuration had been obtained from the aldol reaction to provide **13b**, assembly of the cyclopentenone ring was initiated by a Claisen reaction with lithium *tert*-butyl acetate, which gave the desired β-keto ester **14** in high yield. As expected from the previous results (vide supra), the β-keto ester **14** showed significant keto−enol tautomerism in solution; a peak at 11.8 ppm in the ^{1}H NMR spectrum being assignable to the intramolecularly hydrogen-bonded enol proton. Cyclization of protected β-keto ester **14** was accomplished as outlined in Scheme 4, that is, by a one-pot ozonolysis in methanol followed by direct ozonide reduction (solid supported triphenylphosphine) and Knoevenagel reaction in the presence of potassium carbonate resulting in cyclopentenone **16** in 32% yield. This yield could be increased to 46% using sodium triacetoxyborohydride as reductant after ozonolysis, and no further base was required for the Knoevenagel reaction as this was found to occur spontaneously under these conditions. Despite the fact that this step had considerable room for improvement, the desired cyclopentenone **16** was prepared in sufficient quantity to allow initial attempts to carry out a Michael addition of either an acetylenic or a vinylic nucleophile. A wide variety of conditions were attempted without success, and we surmised that the *tert*-butyl ester may well be too sterically hindered for an already highly substituted ring system. We therefore turned to the preparation of nitrile analogue of ester **2** (Scheme 1), that is, via the sequence shown in Scheme 5.

Scheme 5. Diastereo- and Enantioselective Synthesis of Cyclopentanone **20**



Reaction of phenyl ester **13b** with the lithium anion of acetonitrile provided ketone **17** in near quantitative yield. Subsequent reaction with ozone gave two products which could be separated by chromatography in high combined yield. The main component was the desired cyclopentenone **18**; however, the remaining component (single diastereoisomer) initially looked very similar to **18** by NMR but appeared to have an additional oxygen atom present according to MS. We surmised that it may be the result of intramolecular trapping of the initial fragmentation product (carbonyl oxide) upon transforming the primary ozonide derivative of **17** into the secondary ozonide (by formaldehyde elimination−recombination[16]) by the ketone function. The structure of the *endo*-peroxide **19** was subsequently con-

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(14) Kruger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837−838.
(15) Flack, H. D. *Acta Crystallogr., Sect. A* **1983**, *39*, 876−881.

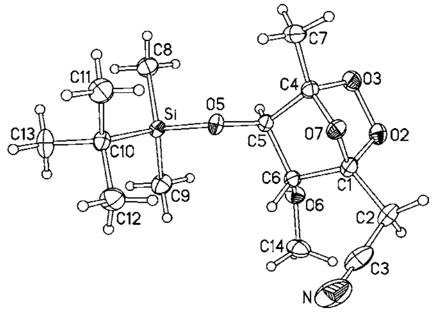

Figure 2. X-ray structure of *endo*-peroxide **19** (50% thermal ellipsoids).

firmed by X-ray crystallography (Figure 2), which also confirmed the relative and absolute stereochemistry of the single diastereoisomer obtained. The *endo*-peroxide **19** could be transformed to the desired cyclopentenone **18** using zinc/HCl reasonably efficiently, and the final two carbons required to access an equivalent of **2** were achieved on this highly unreactive system using a stoichiometric trialkylphosphine vinylcuprate procedure,[17] which produced vinylcyclopentanone **20** in 81% yield as the major diastereoisomer (10:1). NOe studies (see Supporting Information) confirmed the relative stereochemistry as shown by **20** (molecular mechanics model shown in Supporting Information that supports the nOe findings).

The nitrile analogue of cyclopentanone **2** (i.e., **20**) has been prepared in a highly efficient manner, requiring only seven steps, and is the most efficient entry to the type of system reported to date (46% overall yield). Importantly, this synthesis is readily adaptable to access either the indicated absolute stereochemistry or its enantiomer as required. Further derivatization of **20** to access viridenomycin **1** is underway.

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Supporting Information Available: General experimental methods, X-ray crystallographic data for compounds **15** and **19**, and ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via Internet at http://pubs.acs.org.

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(17) (a) Cargill, R. L.; Bushey, D. F.; Ellis, P. D. *J. Org. Chem.* **1974**, *39*, 573−575. (b) Watanabe, H.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2919−2934.