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Pd-Catalyzed Asymmetric Allylic Alkylation. A Short Route to the Cyclopentyl Core of Viridenomycin

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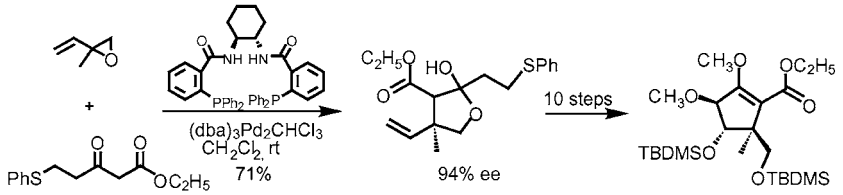
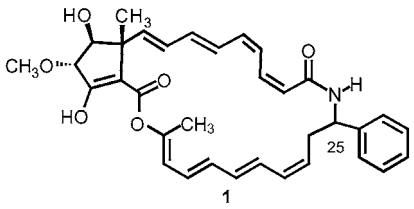
ABSTRACT



A palladium-catalyzed asymmetric allylic alkylation effects a dynamic kinetic asymmetric transformation of racemic isoprene monoepoxide and a surrogate for Nazarov's reagent in which a quaternary center is created with exellent ee. The resultant adduct allows easy access to a substrate for ring-closing metathesis to form a cyclopentenone and sets the stage for an 11-step synthesis of the cyclopentyl core of the antibiotic antitumor agent viridenomycin.

The actinomycete *Streptomyces gannmycicus* produced an antitumor antibiotic designated AL081 that prolonged the survival of mice suffering B16 melanoma.[1] It was established to be identical to viridenomycin.[2] The structure was subsequently established as **1** solely on the basis of detailed NMR



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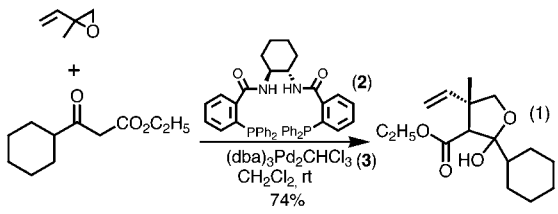
studies. Neither the stereochemistry of C-25 nor the absolute configuration had been established. Synthesis provides a strategy to clarify these structural points and provides access to structural modifications in order to understand biological mode of action of **1** and to design analogues that would have more drug like structural features. Furthermore, the unusual structure provides a challenge for synthesis. First, the densely functionalized cyclopentane ring core also contains a quaternary center, always a formidable task. The high degree of unsaturation of the macrocycle and the presence of an enol ether also constitute difficult structural units. Two groups have embarked upon the synthesis.[3,4] The magnitude of the challenge is highlighted by the fact that the successful syntheses of the cyclopentane core required 20 steps by a strategy utilizing a chiral auxiliary[3] and 32 steps by one employing a starting material from the "chiral pool".[4]

We have recently disclosed a new approach to create quaternary centers asymmetrically by utilizing dynamic kinetic asymmetric transformations (DYKAT) of vinyl epoxides as shown in eq 1.[5] The high regio- (9:1) and



enantioselectivity (99% ee, determined after dehydration) to

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

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

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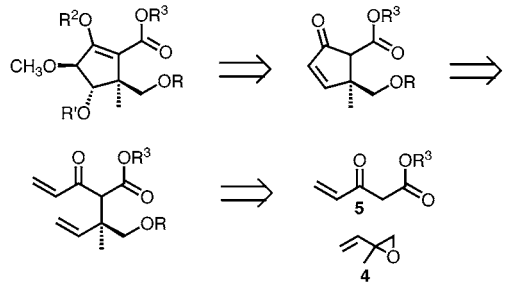
create a quaternary center using our standard ligand **2** in the presence of a Pd(0) source **3** is remarkable. This result allows the formulation of a synthetic strategy toward the cyclopentyl core of viridenomycin as depicted in Scheme 1. The potential

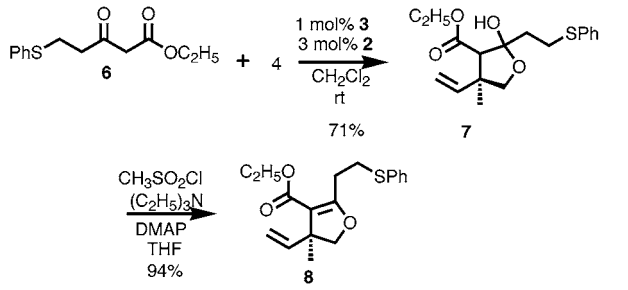
Scheme 1. Retrosynthetic Analysis



availability of the *trans*-diol from an olefin sets the stage for the synthesis of the requisite cyclopentenone via a ring-closing metathesis. Thus, the problem simplifies to isoprene monoepoxide (**4**) and the Nazarov reagent **5**[6] as the starting materials. Unfortunately, the Nazarov reagent kills the Pd(0) catalyst. Believing the ability of this reagent to coordinate Pd(0) was the source of the problem, we turned to a precursor in our synthesis of this reagent[7] that lacked the offending double bond.

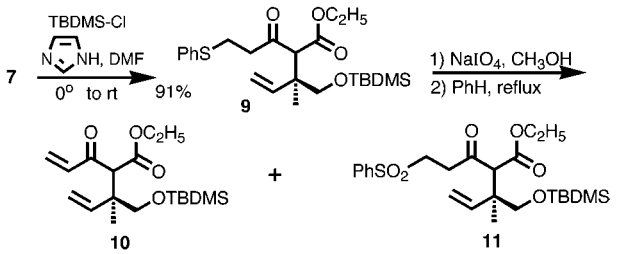
The β-thio derivative **6**, derived by alkylation of the dianion of ethyl acetoacetate, participated without incident in the DYKAT as shown in Scheme 2. The initial adduct **7**

Scheme 2. Dykat



is a mixture of diastereomers. Simple dehydration generates a single dihydrofuran **8**, which was shown to have 94% ee by chiral HPLC analysis. Protection of the primary alcohol derived from the lactol **7** fixed it in the keto form **9** to allow easy elimination of the phenylthio group via sulfoxide thermolysis (see Scheme 3). Oxidation to the sulfoxide with sodium metaperiodate avoids overoxidation. The crude sulfoxide was directly thermolyzed in benzene at reflux to

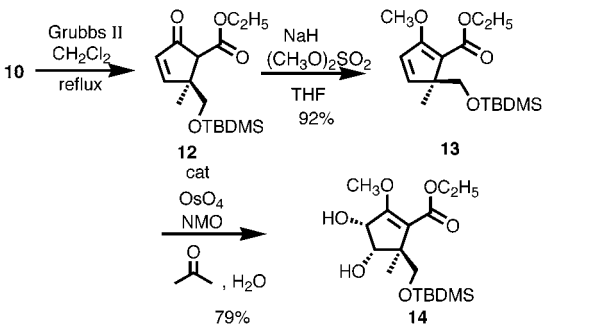
Scheme 3. Diene Formation



give the desired enone in 60% yield.[7] A significant amount (30%) of sulfone **11** was also isolated. The latter presumably derives from conjugate addition of phenylsulfinate anion, which in turn was produced by disproportionation of the phenylsulfenic acid byproduct of the sulfoxide thermolysis. Addition of dihydropyran as a trap for sulfenic acid increased the yield of the enone to 77% accompanied by only 6% of the conjugate adduct **11.** Ethyl vinyl ketone proved even more effective, wherein enone **10** was isolated in 84% yield.

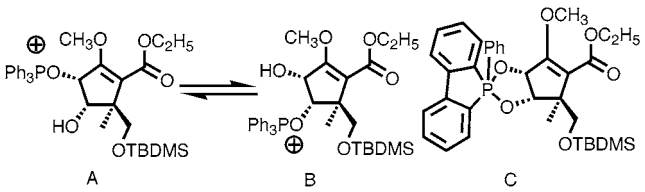
Ring-closing metathesis with the second generation Grubb's catalyst proved to be very slow, requiring 3.5 days to give still only incomplete conversion (see Scheme 4).[8] Fortunately,

Scheme 4. Cyclopentene Synthesis



the cyclopentenone **12** was isolated in a satisfactory yield of 69%, 86% based upon recovered starting material. The derived enol ether **13** of the β-ketoester underwent completely diastereoselective dihydroxylation[9] to give the *cis* diol **14**. The attack *anti* to the more bulky siloxymethyl group was confirmed by a strong NOE between the methine ring hydrogen and the hydrogens of the CH_2OR group.

Completion of the synthesis requires inversion of the allylic alcohol. It was envisioned that a Mitsunobu protocol[10] may provide this chemoselectivity. If the two alkoxyphosphonium species A and B are in dynamic equilibrium through

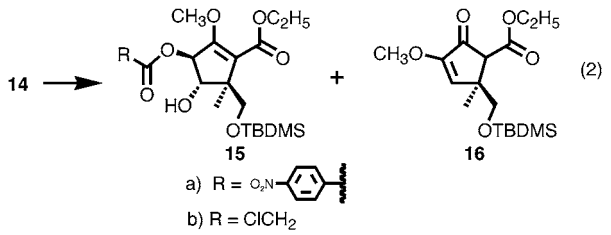


(3) Arrington, M. P.; Myers, A. I. *Chem. Commun.* **1999**, 1371. Kruger, A. W.; Meyers, A. I. *Tetrahedron Lett.* **2001**, *42*, 4301. Waterson, A. G.; Kruger, A. W.; Meyers, A. I. *Tetrahedron Lett.* **2001**, *42*, 4305.

(4) Ishihara, J.; Hagihara, K.; Chiba, K.; Ito, K.; Yanigasawa, Y.; Totani, K.; Tadano, K. *Tetrahedron Lett.* **2000**, *41*, 1771.

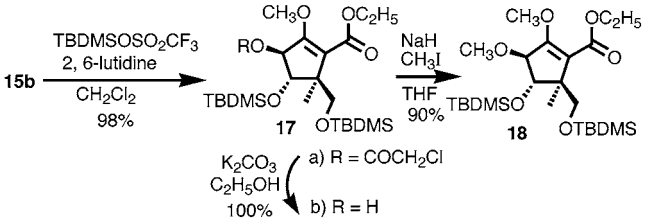
(5) Trost, B. M.; Jiang, C. *J. Am. Chem. Soc.* **2001**, *123*, 12907.

a hypervalent phosphorane, then it would be expected that A would be more reactive because it is allylic and therefore lead preferentially to product. In the event, under standard Mitsunobu conditions (Ph_3P, DEAD, 4-nitrobenzoic acid) two products, **15** and **16**, in addition to recovered starting material were formed (eq 2). The best yield of the desired



p-nitrobenzoate **15a** of 48% was obtained at 40 °C in toluene. The yield increased slightly to 52% by using DIAD instead of DEAD. Changing the acid to chloroacetic acid improved the yield further to 57%. Several alternatives were explored to improve the yield. For example, use of 9-phenyldibenzophosphole as the phosphine for the Mitsunobu reaction led to isolation of the cyclic phosphorane C, which unfortunately would not react further. Reaction of the cyclic *ortho*-aminal formed from diol **14** and the DMF dimethyl acetal[11] also did not lead to any successful reaction. The cyclic sulfite from diol **14** and thionyl chloride also did not lead to any desired product. The byproduct of the Mitsunobu reaction, which accounts for 20−40% of the crude mass, has been tentatively identified as cyclopentenone **16** on the basis of its spectral properties. This product presumably arises by an intriguing skeletal rearrangement involving the homoallyl−cyclopropylcarbinyl−cyclobutenyl cation manifold of the alkoxyphosphonium salt at the neopentyl hydroxy group.[12] The ability of the rearrangement, which involves highly strained intermediates of the bicyclo[2.1.0]pentane and bicyclo[1.1.0]butane type, to compete with an allylic displacement is remarkable. Scheme 5 shows completion of the synthesis which proceeded straightforwardly.

Scheme 5. Completion



The successful use of a surrogate for the Nazarov's reagent in the Pd-catalyzed DYKAT reaction corresponds to the introduction of an asymmetric alkyl group. The usefulness of the reagent for subsequent annulations then makes this asymmetric substituted building block a useful approach for the asymmetric synthesis of cyclic structures. In this particular case, the presence of the two double bonds nicely sets the stage for a ring-closing metathesis. The availability of the heavily functionalized cyclopentyl core of viridenomycin in only 11 steps contrasts sharply with the two existing routes, the shorter of which required nearly twice as many steps. Efforts toward a total synthesis of viridenomycin and to establish the unresolved stereochemical issues are underway.

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Supporting Information Available: Characterization data for **7**−**10**, **12**−**15**, **17**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) A plausible mechanism for the formation of **16** follows.