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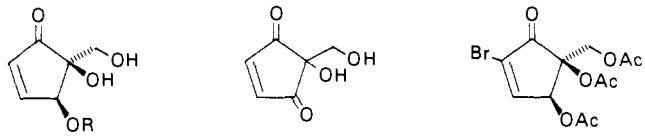
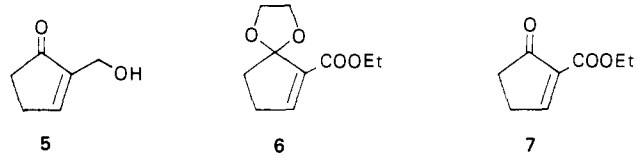
A Stereospecific Total Synthesis of (±)-Pentenomycin I, (±)-Pentenomycin II, and Dehydropentenomycin I Exploiting a Versatile Latent α-Ketovinyl Anion Equivalent

Sir:

In this communication we report an efficient, stereospecific total synthesis of three novel cyclopentenoid antibiotics, pentenomycin I (**1**), pentenomycin II (**2**), and dehydropentenomycin I (**3**) exploiting a versatile latent α-ketovinyl anion equivalent. Pentenomycins I and II were isolated by Umino and co-workers in 1973 from culture broths of *Streptomyces eurythermus* and assigned structures **1** and **2**, respectively, based on a combination of spectroscopic techniques[2] including X-ray crystallographic analysis[3] of the derived bromotriacetate **4**. More recently (1978) Noble et al. reported the isolation of antibiotic G-2201-C (**3**), a simple oxidation product of pentenomycin I, from *Streptomyces cattleya*[4] which we have termed dehydropentenomycin I.[5,6] Our interest in these synthetic

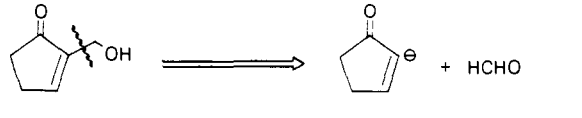


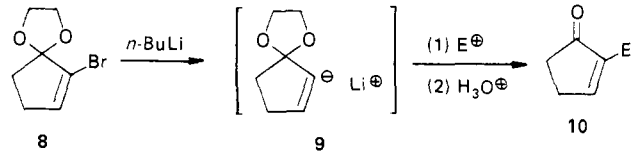


targets was prompted both by their demonstrated activity against Gram-positive[1,4] and Gram-negative[1,4] bacteria including *Neisseria gonarrhoeae*[1] as well as by the potential pharmacological importance of the cyclopentenone structural unit recently suggested to be the reactive functionality in a variety of structurally complex antitumor agents.[7] Our synthetic route is particularly attractive in that it is short, stereospecific, highly efficient (i.e., proceeds in 25, 22, and 11% overall,[8] respectively, for **1–3** from cyclopentenone) and has led to the development of new methodology for α,β-enones.

From a retrosynthetic perspective, α-hydroxymethylcyclopentenone **5** appeared to be an ideal intermediate for the elaboration of **1–3.** Although merely an olefinic positional isomer of the enolic form of α-formylcyclopentanone, examination of the literature revealed, somewhat surprisingly, no previous report for this compound. Furthermore, α-hydroxymethyl-α,β-enones are, in general, not common to the chemical literature. With these considerations in mind we set out to devise a viable approach to **5.**

Initial successful construction of **5**,[9] albeit expensive and multistep, employed the low-temperature Dibal reduction of ketal **6**[9] followed by careful deketalization (HOOCCOOH/aqueous CH_2Cl_2). Ketal **6** in turn was readily available in 82% yield[8] from 2-carbethoxy-2-cyclopentenone (**7**) (1.2 equiv $HOCH_2CH_2OH$/catalyst:$HOOCCH{=}CHCOOH/C_6H_6/-H_2O$ via the Dean-Stark procedure),[10] the latter prepared from commercially available 2-carbethoxycyclopentanone as reported by Reich and co-workers (i.e., α-phenylselenenylation followed by oxidative-elimination).[11] Although available in 53%[8] yield from **7,** the demand for large quantities of **5** coupled with the expense of phenylselenenyl chloride necessitated the development of an alternate route. To this end we envisioned the hypothetical reaction illustrated below. Equivalent to this transformation appeared to be metalation[12] of bromo ketal **8;** addition of CH_2O and deketalization would then afford **5.** Indeed, treatment of **8**[9,13] with *n*-butyllithium (−78 °C, THF)





led to vinyl anion **9**, which could be efficiently captured with a variety of electrophilic reagents; for the case at hand careful addition of predistilled gaseous CH_2O and subsequent deketalization afforded **5** (mp 68–69 °C) in 84% yield.[8,14] *The efficiency of this approach to* **5** *demonstrates, we believe, that*

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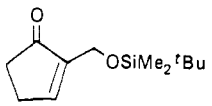
α-bromo ketals hold considerable promise as latent α-keto-vinyl anion equivalents.[15]

With a viable route to **5** secured, we next directed our attention to the completion of our synthetic venture. Central here was elaboration of **13**, a *common* intermediate from which **1–3** could in turn be generated. To this end, cis-hydroxylation of **11**,[9] obtained from **5** in 77%[8] yield (1.1 equiv of *tert*-butyldimethylsilyl chloride/2.2 equiv of imidazole/DMF)[16] with 1.1 equiv of OsO_4 in pyridine,[17] followed by reductive cleavage (aqueous $NaHSO_3$) of the derived osmate ester, afforded cis diol **12**[9] in 95% yield.[8] Dehydrogenation of **12** was then conveniently effected via selenium dioxide oxidation[18] (SeO_2, *t*-BuOH, 7 days, reflux, followed by chromatography on silica gel). Under these conditions crystalline **13**[9] (mp 81 °C) was obtained in 53% yield: IR ($CHCl_3$) 3540 (s, br), 3025 (m), 1725 (s) cm^{-1}; NMR (220 MHz) δ 0.25, 0.29 (s, s, 6 H), 1.08 (s, 9 H), 3.80, 3.98 (br s, AB system, ν_{AB} = 25.6 Hz, J = 10 Hz, 4 H), 5.03 (br s, 1 H), 6.56 (d, J = 6 Hz, 1 H), 7.91 (m, 1 H).



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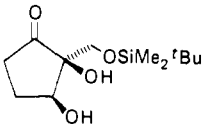

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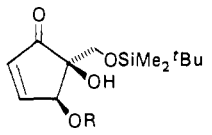
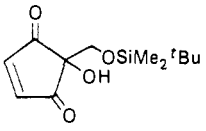


13 (R = H)
14 (R = Ac)



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With **13** in hand, conversion to **1–3** proceeded without event. In particular, hydrolysis of **13** (aqueous AcOH, THF, 80 h, room temperature)[16] afforded (±)-pentenomycin I (96%), while acetylation (Ac_2O, pyridine, 4 °C, 18 h), followed by a similar hydrolysis protocol of the derived monoacetate (**14**),[9] gave (±)-pentenomycin II (85%). Jones oxidation[19] of **13** (1.5 equiv, acetone, −10 °C) on the other hand led to the beautifully crystalline yellow enedione **15**[9] (61%, mp 65 °C) which upon hydrolysis afforded dehydropentenomycin I (74% yield[8] from **15**). That **1–3** were indeed identical with authentic pentenomycin I, pentenomycin II, and dehydropentenomycin I, respectively, was apparent from their spectroscopic properties (IR, 220-MHz NMR, and UV) as well as by direct comparison with published ^1H and, in the case of **3**, ^{13}C NMR spectra. Finally, synthesis of **3** confirms the structure of dehydropentenomycin I.

Studies extending this route to the epimeric series of antibiotics (i.e., antibiotics C-2554 AI, AII, and B),[5] as well as to analogues of this novel class of pharmacologically active cyclopentenones, are currently in progress in our laboratory.

Acknowledgment. It is a pleasure to acknowledge the support of this investigation by the National Institutes of Health (The National Cancer Institute) through Grant No. CA-19033. In addition, we thank Mr. S. T. Bella of the Rockefeller University for the microanalysis and the Middle Atlantic Regional NMR Facility (NIH No. RR542) at the University of Pennsylvania where the 220-MHz NMR spectra were obtained.

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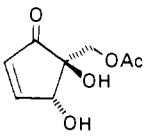

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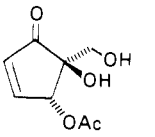

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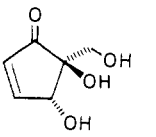

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(6) After the completion of our synthesis of (±)-pentenomycin I, we learned that the Syntex group had completed a synthesis of (−)-pentenomycin I from glucose. We thank Dr. John G. Moffatt for communicating their work to us prior to publication. Their approach was presented at the 9th International Symposium on Carbohydrate Chemistry, London, April 1978, and will appear in *Pure Appl. Chem.*
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(8) All yields recorded here were based on isolated material after purification via distillation, recrystallization, or chromatography (TLC or LC on silica gel).
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(13) Ketal **8** was prepared from 2-cyclopentenone in 74% overall yield[8] via bromination (1.6 equiv of Br_2, CCl_4), dehydrobromination (1.5 equiv of Et_3N, CCl_4), and ketalization (ethylene glycol, TsOH, C_6H_6, $-H_2O$).
(14) Hydroxyenone **5** is a white crystalline solid (mp 68–69 °C): IR ($CHCl_3$) 3620 (m), 3550–3350 (m, br), 1700 (sh), 1690 (s), 1645 (m) cm^{-1}; NMR (220 MHz) δ 2.46 (m, 2 H), 2.65 (m, 3 H), 4.38 (br s, 2 H) 7.71 (m, 1 H).
(15) During the course of this investigation we demonstrated that a variety of simple α-bromo ketals, prepared from the corresponding α-bromo-α,β-enone, underwent efficient metalation and subsequent capture with a variety of electrophilic reagents including alkyl iodides, aldehydes, ketones, ethyl chloroformate, and trimethylsilyl chloride. The results of this study will be forthcoming in the near future.
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Electrochemical Behavior and Standard Potential of Au^- in Liquid Ammonia

Sir:

In a recent paper[1] spectroscopic evidence for the existence of the first transition metal anion, the auride ion (Au^-), produced in liquid NH_3 solution containing cesium, rubidium, or potassium was reported. Preliminary electrochemical studies on the auride ion were described in this work but no detailed electrochemical data were given. We report here the electro-

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