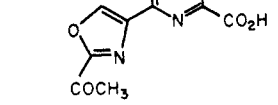
Less randomization of label was found when either the DL or L ^{14}C-labeled serine was added at 72 h, and in both of these 72-h runs the label in berninamycin was accounted for totally by the ^{14}C present in berninamycinic acid and the five pyruvic acid dinitrophenylhydrazone units isolated from each antibiotic molecule. When ^{14}C-labeled serine was added to the cultures at 48 h, somewhat less of the total label was associated with dehydroalanine and berninamycinic acid, probably owing to the metabolic conversion of serine into the other amino acid residues.

These results support the argument that dehydroalanine is synthesized via dehydration of serine rather than dehydrogenation of alanine. However, present results do not determine whether this occurs at the individual amino acid level or following incorporation into a peptide structure.

The specific activity of berninamycinic acid is approximately twice that of the dehydroalanine residues (pyruvic acid dinitrophenylhydrazone), suggesting that two serine residues are incorporated into this unit. One serine residue presumably labels C-5, C-6, and C-6a of berninamycinic acid, which would accord with the recent suggestion[19] that berninamycinic acid arises in sulfomycin from an oxazole precursor (**2**).[20] When



2

L-[U-^{14}C]cysteine was incubated with *S. bernensis*, berninamycin was labeled, but, following degradation, almost no label was found in pyruvic acid dinitrophenylhydrazone (dehydroalanine), excluding the possibility that dehydroalanine is derived from cysteine. Essentially all of the label was in the berninamycinic acid residue, presumably in the thiazole (dehydrocysteine) portion (C-2, C-3, C-11). These results suggest that one of the serine units found in berninamycinic acid had been converted into cysteine and incorporated into berninamycin as described.

The observation that dehydroalanine is derived from dehydration of serine argues for a similar origin of other unsaturated residues in berninamycin as well as of the dehydroalanine residues in other antibiotics.[1-7] Thus, it can be postulated that oxazole A is biosynthesized from one threonine and one serine residue and oxazole B from two threonine residues. These possibilities are under investigation, as are the identities of the carbons labeled by serine and cysteine in berninamycinic acid.

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A New Bisannulation Reagent Easily Prepared from a Butadiene Telomer, and Its Application to Steroid Synthesis

Sir:

We introduce 1,7-octadien-3-one (**4**) as an easily available and very convenient bisannulation reagent. Annulation reaction to form fused six-membered cyclic ketones using alkyl vinyl ketones or their equivalents is well known as the Robinson annulation[1] and has wide application, particularly for stepwise construction of polycyclic compounds such as steroids and certain terpenoids.[2] One important offshoot of the Robinson procedure is the construction of two fused six-membered cyclic ketones from one reagent, instead of repeating the common Robinson cyclization twice. This new method of cyclization is called bisannulation, and few compounds have been recommended for this purpose. According to Danishefsy,[3] the bisannulation reagent is a synthetic equivalent to 7-octene-2,6-dione. In other words, the bisannulation reagent must have a terminal enone or its equivalent in one side and a masked ketone to generate a 1,5-diketone system in the other end of the molecule. As the masked ketone, Stork's isoxazole[4] and Danishefsky's 6-vinyl-2-picoline[3,5] are well known. The usefulness of the bisannulation reagent is determined by easy accessibility of the reagent itself and the facile procedure of unmasking. For example, the isoxazole ring is unmasked by hydrogenation and base-catalyzed hydrolysis. Birch reduction, followed by acid-catalyzed hydrolysis is the method of converting the picoline into 1,5-dione.

The new bisannulation reagent, 1,7-octadien-3-one, that we now introduce, is very easily prepared in high yield from butadiene. After initial Michael reaction at the enone moiety, the terminal double bond is converted into the desired methyl ketone in one step by palladium-catalyzed oxidation in high yield under mild conditions as shown below.[6] Thus, this compound is the most cheaply and easily available, convenient bisannulation reagent.

We are actively working on synthetic uses of butadiene telomers[7] easily prepared in one step by the palladium-catalyzed reactions of butadiene with various nucleophiles.[8] Reaction of butadiene with acetic acid catalyzed by $Pd(OAc)_2$ and PPh_3 affords 3-acetoxy-1,7-octadiene (**1**) and 1-acetoxy-2,7-octadiene (**2**) in high yield.[9] The acetate **2** can be rearranged to **1** by the palladium catalyst. The acetate **1** was hydrolyzed to the alcohol **3**, which was dehydrogenated by gas-phase reaction catalyzed by Cu/Zn alloy[10] at 360 °C to give the desired enone **4** in high yield (Scheme I): bp 31 °C (4 mmHg), semicarbazide mp 180–182 °C.

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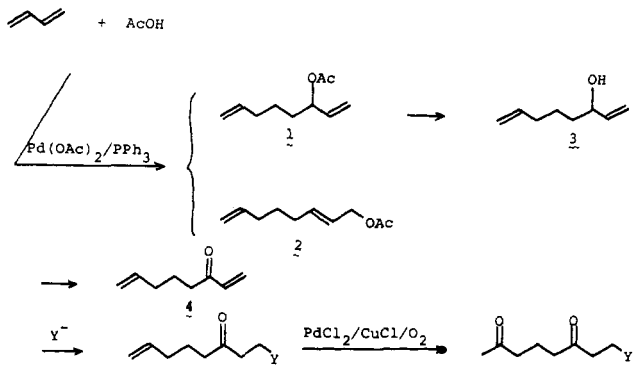
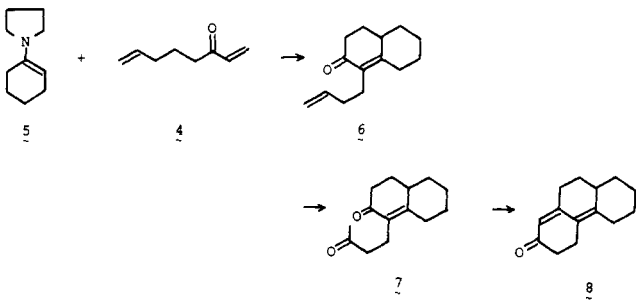
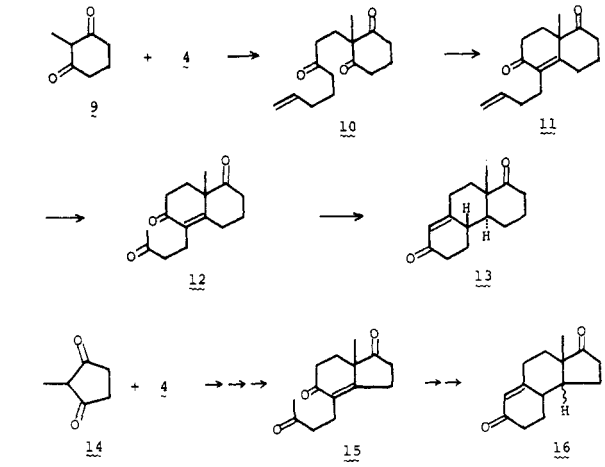
Scheme I



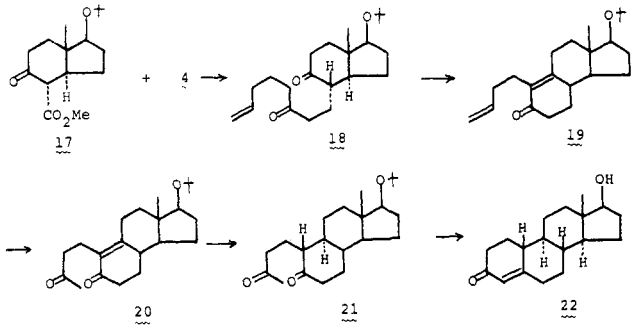
Scheme II



Scheme III



Scheme IV



At first, the bisannulation of cyclohexanone was carried out. The Michael reaction of the enone **4** with the enamine **5** was carried out in boiling dioxane. Hydrolysis of the enamine and subsequent aldol condensation took place by the treatment with hydrochloric acid to give the butenyloctalone **6** in 64% yield: bp 99–101 °C (3.5 mmHg); IR 1665, 1640, 1612, 912 cm^{-1}; NMR (CCl_4) δ 4.7–6.1 ppm (3 H, m, vinyl); MS *m/e* 204 (M^+). The oxidation of the terminal double bond of **6** was carried out by shaking a mixture of **6** (1.23 g, 6.05 mmol), $PdCl_2$ (177 mg, 1 mmol), and CuCl (10 mmol) in aqueous DMF under an oxygen atmosphere at room temperature for 24 h to give the diketone **7** in 83% yield: bp 122–129 °C (3.5 mmHg); IR 1712, 1663, 1612 cm^{-1}; NMR (CCl_4) δ 2.02 ppm (3 H, s, CH_3). Finally the diketone **7** was cyclized using potassium 2-methyl-2-butoxide in dry toluene at room temperature to give the tricyclic ketone **8** in 73% yield (Scheme II): mp 64.5–65.5 °C, lit.[3] mp 59–60 °C; MS *m/e* 202 (M^+).

The important tricyclic intermediates (**13** and **16**) of steroid synthesis were prepared from 2-methyl-1,3-cyclohexanedione (**9**) and 2-methyl-1,3-cyclopentanedione (**14**) (Scheme III). Michael addition of **9** to **4** took place using triethylamine in ethyl acetate to give the triketone **10** in 80% yield: NMR (CCl_4) δ 1.10 ppm (3 H, s, CH_3). The aldol condensation proceeded in refluxing acetonitrile using β-alanine and 1 N perchloric acid for 7 days to give the bicyclic diketone **11** in 73% yield: IR 1715, 1665, 920 cm^{-1}; NMR (CCl_4) δ 1.31 ppm (3 H, s, CH_3).[11] Then the terminal double bond was oxidized with $PdCl_2$/CuCl to give the triketone **12** in 75% yield: IR 1710, 1663 cm^{-1}; NMR (CCl_4) δ 1.40 (3 H, s, CH_3), 2.10 ppm (3 H, s, CH_3CO). Hydrogenation catalyzed by palladium on carbon in ethyl acetate–triethylamine, followed by the aldol condensation catalyzed by sodium hydroxide, afforded the transfused tricyclic dione **13** in 92% yield:[12] mp 122–123 °C, lit.[13] mp 122 °C. The similar reaction sequence was repeated with 2-methyl-1,3-cyclopentanedione (**14**) to give the trione **15**: mp 96–97 °C, lit.[13] mp 93–94.5 °C. The trione was converted into **16**.[14]

The synthesis of (+)-19-nortestosterone was then carried out. The optically active keto ester **17**, $[\alpha]^{25}_D$ +35.1° (*c* 1.10, $CHCl_3$), prepared by methylation of the corresponding optically active keto acid,[2d,15] was subjected to Michael reaction with the enone **4** in benzene using sodium hydride as a catalyst. Then the ester group was removed by heating at 160 °C in aqueous HMPA with sodium iodide to give the diketone **18** in 68.4% yield:[16] $[\alpha]^{25}_D$ +23.8° (*c* 0.992, $CHCl_3$); IR 1710, 1461, 908 cm^{-1}; NMR (CCl_4) δ 1.00 (3 H, s, CH_3), 1.10 ppm (9 H, s, $C(CH_3)_3$). The aldol condensation was carried out by sodium hydroxide in aqueous ethanol to give **19** in 90% yield: $[\alpha]^{25}_D$ −14.8° (*c* 0.61, $CHCl_3$); IR 1668, 910 cm^{-1}; NMR (CCl_4) δ 0.85 (3 H, s, CH_3), 1.10 ppm (9 H, s, $C(CH_3)_3$). The palladium-catalyzed oxidation of the terminal double bond afforded the diketone **20** in 78% yield: $[\alpha]^{25}_D$ −18.1° (*c* 1.02, $CHCl_3$); IR 1710, 1668 cm^{-1}; NMR (CCl_4) δ 0.83 (3 H, s, CH_3), 1.13 (9 H, s, $C(CH_3)_3$), 2.05 ppm (3 H, s, $COCH_3$). Then the internal double bond was reduced using palladium on carbon in ethanol containing triethylamine to give **21** in 95% yield: $[\alpha]^{25}_D$ −22.5° (*c* 1.86, $CHCl_3$); IR 1718 cm^{-1}; NMR (CCl_3) δ 0.75 (3 H, s, CH_3), 1.09 (9H, s, $C(CH_3)_3$), 2.03 ppm (3 H, s, CH_3CO). Finally the aldol condensation and hydrolysis of the *tert*-butyl ether group were achieved by refluxing in methanolic hydrochloric acid to give (+)-19-nortestosterone (**22**) in 76% yield (Scheme IV),[17] which was identified by its mp 110–111 °C (lit.[18] mp 111–112 °C), rotation $[\alpha]^{25}_D$ +57.8° (*c* 0.526, $CHCl_3$) (lit.[14] $[\alpha]^{25}_D$ +58.7°), and ^{13}C NMR. Syntheses of steroids having different functionalities and asymmetric synthesis using 1,7-octadien-3-one are under active investigation.

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A Simple Total Synthesis of (±)-Zearalenone by Intramolecular Alkylation Using a Butadiene Telomer as a Building Block

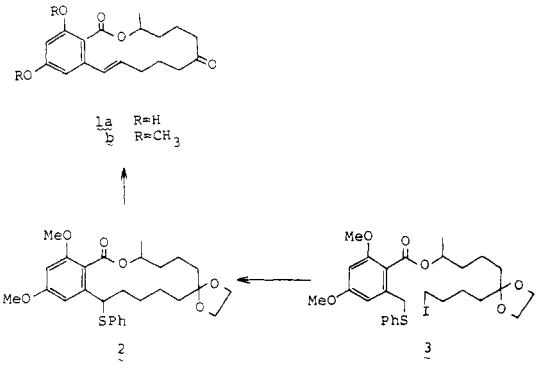
Sir:

Zearalenone (**1a**) is a naturally occurring 14-membered orsellinic acid type macrolide.[1] Two total syntheses of zearalenone were carried out about ten years ago.[2] In their multistep syntheses of the seco acid, the double bond was introduced by applying the Wittig reaction, which did not give the required trans double bond selectively. In addition, the seco acid was cyclized by intramolecular esterification methods, but the yields of the lactonization were very low (31 and 8%). Recently remarkable progress in macrolide formation by the intramolecular esterification has been made.[3] Corey[4] and Masamune[5] carried out partial synthesis of zearalenone from the seco acid in satisfactory yields (75 and 90%) by applying their own activation methods of carboxylic acids.

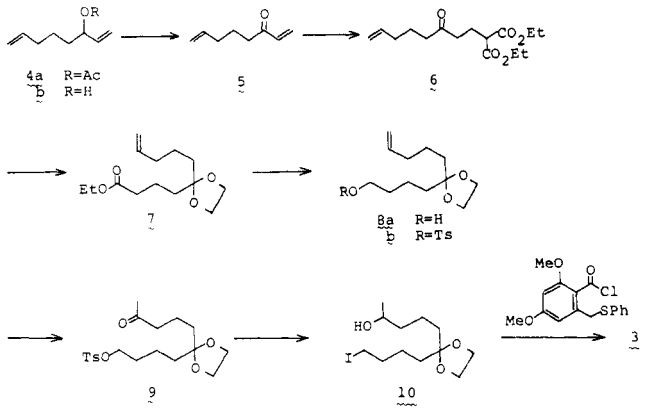
We recently introduced a new efficient method of macrolide formation based on intramolecular alkylation of ω-haloalkyl phenylthioacetates,[6] and the method was successfully applied to the total syntheses of recifeiolide and 9-decanolide. Also lasiodiplodin, a 12-membered orsellinic acid type macrolide, was synthesized.[7] In addition to the efficient intramolecular alkylation method, another characteristic feature in these macrolide syntheses is the use of butadiene telomers obtained by the palladium-catalyzed reaction of butadiene with nucleophiles as convenient starting materials.

We describe herein the simple total synthesis of the dimethyl ether of zearalenone (**1b**) based on the intramolecular alkylation of the carbanion generated from ω-iodoalkyl 2-phenylthiomethyl-4,6-dimithoxybenzoate (**3**) (Scheme I). This method of cyclization requires short reaction time and no high dilution conditions, and gives a satisfactory yield of the macrolides **2**.[8] The phenylthio group can be utilized not only for the activation of the carbanion, but also for the selective introduction of the trans double bond in **1**. In addition, we found that the telomer **4a**, easily prepared by the palladium-catalyzed telomerization of butadiene with acetic acid,[9] is an extremely useful building block of the carbon chain of **1**. The telomer **4a** was hydrolyzed to the allylic alcohol **4b**, which was converted into 1,7-octadien-3-one (**5**) by gas-phase dehydrogenation catalyzed by Cu/Zn alloy.[10] The double bond at C_1 is used for two-carbon elongation by Michael addition of malonate. Above all, the ketone group in **5** is located at the exactly right position for the synthesis of the macrolide **1**. With these suitable functionalities already present in **5**, the ester **3** required for the cyclization was prepared easily by the sequence shown in Scheme II. The Michael addition of diethyl malonate to **5** catalyzed by sodium ethoxide at 0 °C gave 6 in 70% yield: IR (neat) 1730, 910 cm^{-1}; NMR (CCl_4) δ 1.25 (t, J = 7.0 Hz, 6 H, CH_3), 3.30 (t, J = 7.0 Hz, 1 H, $CHCO_2$), 4.16 (q, J = 7.0 Hz, 4 H, OCH_2). One of the ester group was removed (79% yield) by heating at 180 °C in HMPA containing NaI and water, and the ketone was protected as ketal to give **7** in 80% yield: NMR (CCl_4) δ 3.76 (s, 4 H, OCH_2CH_2O). The ester was reduced ($LiAlH_4$, 74% yield) to the alcohol **8a** and converted into tosylate **8b** in 84% yield: NMR (CCl_4) δ 2.43 (s, 3 H, $PhCH_3$), 3.83 (s, 4 H, OCH_2CH_2O). The terminal olefin was oxidized with $PdCl_2/CuCl/O_2$ in aqueous DMF[11] to give the methyl ketone **9** in 70% yield: IR (neat) 1715 cm^{-1}; NMR (CCl_4) δ 2.20 (s, 3 H, CH_3CO), 3.91 (t, J = 5.9 Hz, 2, H, CH_2-OTs). The ketone was reduced ($NaBH_4$, 98% yield) to the alcohol, and the tosylate was converted into the iodide **10** in 94% yield by treatment with sodium iodide in acetone: IR (neat) 3450 cm^{-1}; NMR (CCl_4) δ 3.14 (t, J = 7.0 Hz, 2 H,

Scheme I



Scheme II



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