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

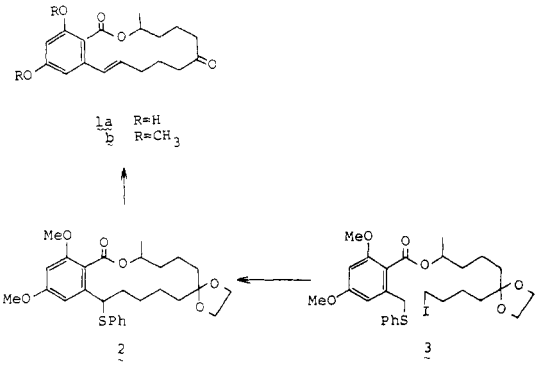
Sir:

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.

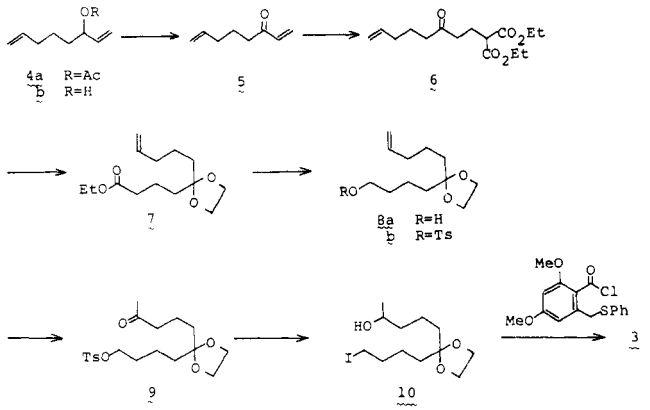
We recently introduced a new efficient method of macrolide formation based on intramolecular alkylation of ω-haloalkyl phenylthioacetates,[6] and the method was successfully applied to the total syntheses of recifeiolide and 9-decanolide. Also lasiodiplodin, a 12-membered orsellinic acid type macrolide, 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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CH_2I). The alcohol **10** was acylated with 2-phenylthiomethyl-4,6-dimethoxybenzoyl chloride[7] to give ester **3** in 90% yield: IR (neat) 1710, 1610 cm^{-1}; NMR (CCl_4) δ 1.29 (d, J = 6.0 Hz, 3 H, CH_3), 3.11 (t, J = 7.2 Hz, 2 H, CH_2I), 3.65 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.82 (s, 4 H, OCH_2CH_2O), 4.07 (s, 2 H, CH_2S), 4.85–5.30 (m, 1 H, CHOCO), 6.28 (br s, 2 H, aromatics), 7.00–7.40 (br s, 5 H, aromatics).

The cyclization of **3** was carried out by the following way. The ester **3** (218 mg, 0.35 mmol) in THF (7 mL) was added slowly over 1.6 h at 40 °C under a nitrogen atmosphere to potassium hexamethyldisilazane (1.05 mmol) in THF (18 mL). The reaction mixture was stirred for 15 min and quenched. The 14-membered lactone **2** was isolated as an oil in 85% yield after chromatographic purification (silica gel): IR (neat) 1720, 1615 cm^{-1}; NMR (CCl_4) δ 1.24 (d, J = 6.0 Hz, 3 H, $CHCH_3$), 3.71 (s, 7 H, OCH_3 and OCH_2CH_2O), 3.74 (s, 3 H, OCH_3), 4.10–4.60 (m, 1 H, CHS), 4.95–5.43 (m, 1 H, OCH), 6.18 (d, J = 2.6 Hz, 1 H, aromatic), 6.80 (d, J = 2.6 Hz, 1 H, aromatic), 6.94–7.14 (m, 5 H, aromatics); MS m/e 470 (M^+). Oxidation of **2** with sodium periodate[12] and subsequent toluene reflux without purification for 20 min produced the ketal of **1b** in 80% yield which was hydrolyzed (aqueous p-TsOH in ether) to give in 84% yield the dimethyl ether of zearalenone (**1b**): mp 124–126 °C (lit.[2a] 124–126 °C); IR (KBr) 1720, 1600, 1165 cm^{-1}; NMR ($CDCl_3$, 100 MHz) δ 1.33 (d, J = 6.0 Hz, 3 H, CH_3), 1.90–2.90 (m, 6 H, $=CCH_2$, CH_2CO), 3.79 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 5.06–5.46 (m, 1 H, HCO), 5.95 (ddd, J = 4.5, 9.5, 16.5 Hz, 1 H, olefinic), 6.35 (d, J = 1.5 Hz, 1 H, aromatic), 6.38 (dd, J = 1.5, 16.5 Hz, 1 H, olefinic), 6.58 (d, J = 1.5 Hz, 1 H, aromatic); MS m/e 346 (M^+). Anal. Calcd: C, 63.14; H, 5.30. Found: C, 63.58; H, 5.10. The trans configuration of the double bond was fully confirmed by the NMR spectrum.

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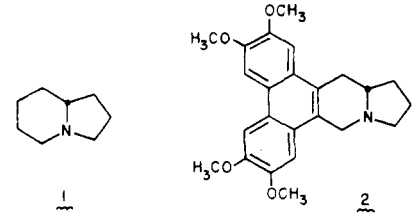
Alkaloid Synthesis by the Intramolecular Imino Diels–Alder Reaction. δ-Coniceine and Tylophorine

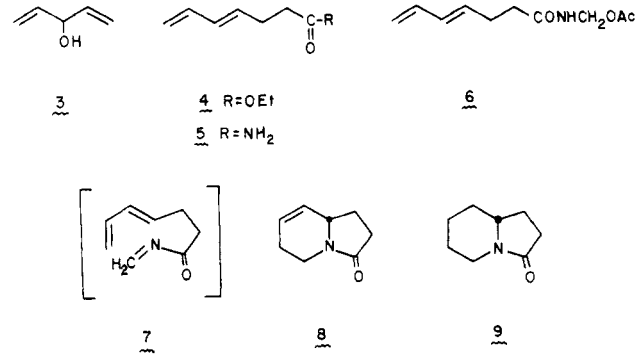
Sir:

The Diels–Alder cycloaddition of conjugated dienes with imino dienophiles, a reaction which has been known for over 35 years,[1] would appear to possess tremendous potential for construction of nitrogeneous natural products. However, this potential has not been realized,[2] perhaps for two reasons: (1) imino dienophiles are inherently unsymmetrical and thus the [4 + 2] cycloaddition with unsymmetrical dienes introduces both regiochemical and stereochemical problems which have only recently been examined;[3] (2) imino Diels–Alder reactions are often sluggish compared with the corresponding "all carbon" cases and may require high reaction temperatures, pressures, and/or Lewis acid catalysts. It seemed to us that both of these drawbacks might be obviated in the intramolecular version of the reaction. Such a strategy has been ignored to date.[4] We now report an initial demonstration of the feasibility of this approach as applied to total synthesis of the two indolizidine alkaloids, δ-coniciene (**1**)[5] and tylophorine (**2**).[6]



1 **2**

The starting material for synthesis of δ-coniceine was divinylcarbinol (**3**), which on treatment with triethyl orthoacetate containing a catalytic amount of propionic acid (130–135 °C, 20 h) gave diene ester **4** in 58% yield after chromatography.[7,8] After a benzene solution of **4** containing 1.5 equiv of dimethylaluminum amide was heated for 1.5 h, carboxamide **5** was



3 **4** R=OEt **6**
5 R=NH_2
7 **8** **9**

formed in 70% yield (mp 94–95 °C).[9] This amide was converted into the corresponding methylol (37% aqueous HCHO, 5% NaOH, glyme),[10] which without purification was transformed into the crystalline acetate **6** using acetic anhydride–pyridine at room temperature (83% from **5**; mp 38–39 °C).[7] A toluene solution of methylol acetate **6** was rapidly passed through a 15-cm column of glass helices maintained at 370–390 °C, and evaporation of solvent afforded essentially pure bicyclic lactam **8** (73%; IR ($CHCl_3$) 1675 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.7 (2 H, br s)). This cyclization presumably occurs via the unstable intermediate acylimine **7**. The double bond[11] of **8** was reduced (5% Pd/C, ethyl acetate, 1 atm) to afford the known[5c] lactam **9** (95%, IR ($CHCl_3$) 1670 cm^{-1}).[7] Reduction of **9** with diborane as described[5c] gave racemic δ-coniceine (**1**) which had the same IR and ^1H NMR spectrum as an authentic sample[12] (picrate mp 227–231 °C, lit. mp 233–234 °C,[13a] 224–228 °C[13b]).

Our synthesis of tylophorine (**2**) began with the readily available ester **10**[6a] which was reduced with $LiAlH_4$–THF to

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