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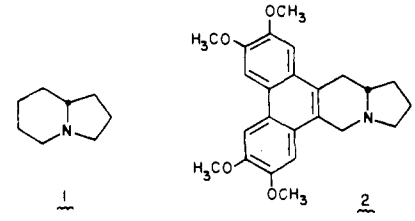
Alkaloid Synthesis by the Intramolecular Imino Diels–Alder Reaction. δ-Coniceine and Tylophorine

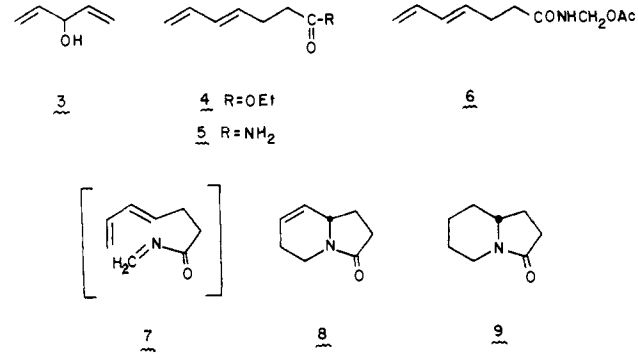
Sir:

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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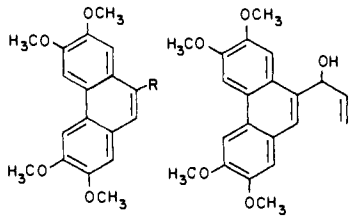
alcohol **11** and oxidized with pyridinium chlorochromate[15] to afford aldehyde **12** (78% from **10**; mp 218–219 °C).[7] Addition of vinyllithium to aldehyde **12** in THF at room temperature produced the allylic alcohol **13** (82%; mp 151–152 °C),[7] which

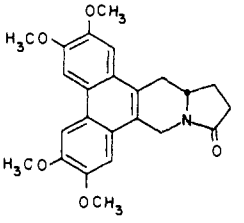


10 R=COOCH$_3$
11 R=CH$_2$OH
12 R=CHO

13

14 R=OEt
15 R=NH$_2$
16 R=NHCH$_2$OAc

underwent the orthoester Claisen rearrangement[8] (CH$_3$C(OEt)$_3$-propionic acid, 130–135 °C, 2 h) to afford ester **14** (84%; mp 97–98 °C).[7] Amide **15** was formed in 80% yield by treatment of ester **14** with 3.5 equiv of dimethylaluminum amide[9] in refluxing methylene chloride (mp 213–214 °C; IR (CHCl$_3$) 3550, 3425, 1680 cm^{-1}). This amide was treated first with a mixture of 37% aqueous formaldehyde–5% NaOH–glyme at room temperature and then with acetic anhydride–pyridine to afford crystalline acetate **16** in 60% isolated yield (mp 155–156 °C; IR (CHCl$_3$) 3540, 1740, 1695 cm^{-1}). Pyrolysis of this acetate in bromobenzene at 220 °C for 5 h yielded the known[6a] pentacyclic lactam **17**[17] (50%; mp 263 °C, lit.[6a] mp 273 °C).[7] The lactam carbonyl of **17** was reduced with



17

LiAlH$_4$ in THF at room temperature to produce racemic tylophorine (**2**, 64%) identical with an authentic sample[15] (IR, UV, MS, ^{1}H NMR).

We are currently exploring the scope of the intramolecular imino Diels–Alder reaction for synthesis of other alkaloids and are also actively investigating the stereochemical parameters of the reaction. This work will be reported shortly.

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(15) We thank Dr. N. B. Mulchandani for a generous sample of natural tylophorine.
(16) Fellow of the A. P. Sloan Foundation, 1975–1979. Recipient of a Research Career Development Award (HL00176) from the National Institutes of Health. Address correspondence to The Pennsylvania State University.
(17) NOTE ADDED IN PROOF. Our lactam **17** was identical with an authentic sample provided by Dr. R. E. Summons. We also thank Dr. A. J. Liepa for providing spectra of compound **17**.

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Titanium-Catalyzed Olefin Metathesis

Sir:

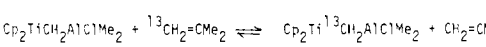
The methylenetitanium complex, Cp$_2$TiCH$_2$AlClMe$_2$ (**1**),[1] catalyzes a metathesis process in which the methylene groups of isobutene and methylenecyclohexane exchange (eq 1). This

(1)

catalyst is selective for exchange of terminal methylene groups and provides strong evidence for an alkylidene/metallacycle mechanism like that now generally accepted for olefin metathesis with conventional catalysts.[2]

Previously we reported that ethylene reacts with a solution of **1** in toluene to form propylene by transfer of a CH$_2$ group from titanium to the olefin.[1] In contrast, isobutene did not seem to interact with **1** under these conditions other than apparently to stabilize it against decomposition at elevated temperatures. Now, labeling studies indicate that the methylene group of **1** *exchanges* with isobutene and that this exchange provides the mechanism for the metathesis reaction described above.

A solution of 0.25 mmol of **1** and 0.5 mmol of ^{13}CH$_2$=CMe$_2$[3] in benzene-d_6 (0.6 mL) was examined perically by ^{1}H and ^{13}C NMR. The spectra show depletion of ^{13}CH$_2$=CMe$_2$ with growth of ^{12}CH$_2$=CMe$_2$ and Ti^{13}CH$_2$. Carbon-13 enrichment is limited to the TiCH$_2$ group (eq 2).



(2)

The exchange of CH$_2$ groups approaches equilibrium in 30 h at 52 °C. Under these conditions, the solution seems stable for 4 days. Approximately 20% of the organometallic decomposes over 8 days, but the amount of isobutene is constant during this time. Methylene exchange catalysis persists beyond 8 days.[4]

Similar experiments were carried out with deuterium-labeled reagents and were monitored by ^{1}H and ^{2}H NMR. In the reaction of (C$_5$H$_5$)$_2$TiCD$_2$AlCl(CD$_3$)$_2$[5] with CH$_2$=C(CH$_3$)$_2$, or (C$_5$H$_5$)$_2$TiCH$_2$AlCl(CH$_3$)$_2$ with CD$_2$=C(CH$_3$)$_2$,[3] exchange is limited to hydrogens connected

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