or, in the absence of added ligand,

$$3[Pt(PPh_3)_2] \xrightarrow{fast} 2[Pt(PPh_3)_3] + Pt \quad (7)$$

Further support for this interpretation is provided by the following observations. (1) Deuterium-labeling experiments using various isotopic mixtures demonstrated conclusively that the reductive elimination is *intramolecular*. Thus, complete decomposition of an equimolar mixture of $[PtH(CH_3)(PPh_3)_2]$ and $[PtD(CD_3)(PPh_3)_2]$ yielded predominantly CD_4 and CH_4 ($[CD_4]:[CD_3H] \gtrsim 20:1$, determined mass spectrometrically); similarly an equimolar mixture of $[PtH(CD_3)(PPh_3)_2]$ and $[PtD(CH_3)(PPh_3)_2]$ yielded predominantly CH_3D and CD_3H ($[CD_3H]:[CD_4] \gtrsim 25:1$). (2) Comparison of the rates of decomposition of $[PtH(CH_3)(PPh_3)_2]$ and $[PtD(CH_3)(PPh_3)_2]$ revealed an appreciable normal primary isotope effect, i.e., $k_1^H/k_1^D = 3.3 \pm 0.3$.

Similar results were obtained for the corresponding complexes of several para-substituted triarylphosphines, $[PtH(CH_3)(PR'_3)_2]$, where $R' = p\text{-}XC_6H_4$. The rates of reaction ($10^4 k_1$, s^{-1}, at -25 °C) decreased along the sequence $R' = p\text{-}ClC_6H_4$ (9.2) > C_6H_5 (4.5) > $p\text{-}CH_3C_6H_4$ (1.4) > $p\text{-}CH_3OC_6H_4$ (0.47). This sequence is consistent with the expected increasing tendency of electron-withdrawing substituents on the phosphine ligands to stabilize platinum(0) and, hence, to increase the driving force for the reductive elimination reaction 1.

Similar experiments on $[PtH(C_2H_5)(PPh_3)_2]$ demonstrated the analogous reductive elimination of C_2H_6, with $k_1 = 9 \times 10^{-4}$ s^{-1} at -25 °C (i.e., ca. twice the corresponding rate for the methyl compound). Preliminary rate measurements on several other $[PtH(R)(PPh_3)_2]$ compounds revealed the qualitative sequence of decreasing reactivity: $R = C_6H_5 > C_2H_5 > CH_3 > CH_2CH{=}CH_2$.

The initial product of the reductive elimination reaction 1, i.e., $[Pt(PPh_3)_2]$, has previously been identified as an intermediate in the substitution and oxidative addition reactions of platinum(0) complexes,[12-14] e.g.,

$$[Pt(PPh_3)_3] \overset{-PPh_3}{\rightleftharpoons} [Pt(PPh_3)_2] \overset{RC{\equiv}CR}{\rightleftharpoons} [Pt(PPh_3)_2(RC{\equiv}CR)] \quad (8)$$

The facile intramolecular reductive elimination of CH_4 from $[PtH(CH_3)(PPh_3)_2]$ at temperatures as low as -25 °C clearly demonstrates not only that the process is thermodynamically favorable but that the kinetic barrier is low. The reverse process, i.e., the oxidative addition of CH_4 to $[Pt(PPh_3)_2]$ (or to $[Pt(PPh_3)_3]$ via $[Pt(PPh_3)_2]$ which is readily derived thereform by dissociation) *must, accordingly, be precluded on thermodynamic rather than on kinetic grounds*. This conclusion is of some significance in the context of the widespread current interest in the catalytic activation of saturated hydrocarbons and suggests that oxidative addition (at least with such mononuclear complexes) is not a promising approach.

Further studies along these lines, including extensions to other hydridoalkylplatinum(II) complexes as well as to corresponding complexes of other metals, notably palladium(II) and nickel(II), are in progress.

Acknowledgments. Support of this research through a grant from the National Science Foundation is gratefully acknowledged. One of us (L.A.) thanks Montedison Co. for a leave of absence.

References and Notes

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(14) The isolation of solid "$[Pt(PPh_3)_2]$", prepared through a route related to that of reactions 2 and 1 has previously been claimed.[15] All subsequent attempts to prepare this compound in monomeric form under conditions where it is sufficiently stable for direct detection and characterization, either in solution or as a solid, appear to have failed. Related monomeric platinum(0) complexes of other (more bulky) phosphines, e.g., $[Pt(P(cyclohexyl)_3)_2]$ and $[Pt(P(i\text{-}Pr)_3)_2]$ have, however, been isolated and unequivocally characterized.[16]
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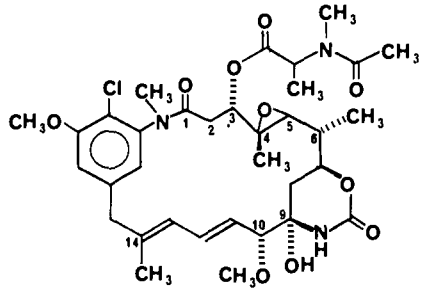
Total Synthesis of (±)-*N*-Methylmaysenine[1]

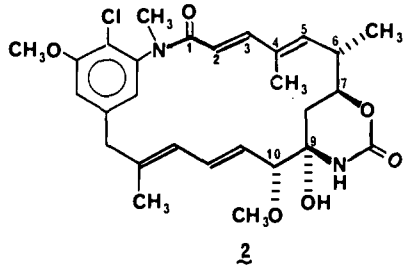
Sir:

Maytansine (**1**) is a promising antitumor agent which is now in phase II of clinical studies with human patients. The isola-



1

tion and determination of structure of this interesting substance by Kupchan et al.[2,3] are among the most notable of recent developments in the field of organic natural products. Because of the extreme scarcity of maytansine and its congenors (e.g., *N*-methylmaysenine (**2**), or maysine which is the 4,5-oxide of



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N-methylmaysenine), and the therapeutic promise of maytansine, there has been considerable interest in maytansenoid synthesis; a number of groups have reported initial studies and good progress in this area.[4] This communication describes the

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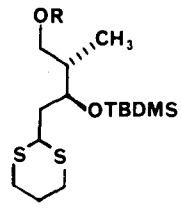
first total synthesis of a maytansenoid, (±)-*N*-methylmaysenine (i.e., (±)-4,5-deoxymaysine) (**2**).

The dithiane **3** and the aldehyde **5** are readily available by stereospecific and efficient routes which have already been described.[4c,5] Conversion of **3** to the 2-methoxy-2-propyl ether **4** was accomplished quantitatively by treatment with 2-



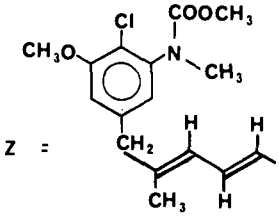
Z — CHO

5

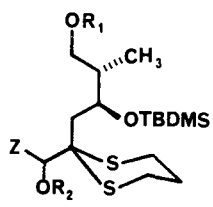
3, R = H

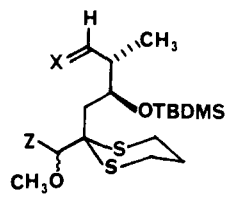
4, R = $C(OCH_3)(CH_3)_2$

TBDMBS = t-Bu—Si(CH₃)₂—



methoxypropene[6] (4 equiv) and a catalytic amount of phosphorus oxychloride in methylene chloride at 0 °C for 30 min followed by isolation (Et_3N quench, dilution with pentane, drying over K_2CO_3, and concentration), R_f 0.17 and 0.51 for **3** and **4** (2:1 pentane–ether, silica gel).[7] Reaction of **4** with 1 equiv of *n*-butyllithium and 1 equiv of *N,N'*-tetramethylenediamine (TMEDA) in tetrahydrofuran (THF) initially at −78 °C and then at −24 °C for 1.5 h afforded the 2-lithiodithiane species which after removal of most of the THF and TMEDA in vacuo (−24 °C), replacement by toluene, and coupling to the aldehyde **5**[5] (6–7 min at −78 °C) gave the adduct **6** (90% yield) as a mixture (~55:45) of diastereomers at C-10 (maytansine numbering). This product routinely was used directly in the next step of the synthesis.[8] However, the diastereomeric diols obtained by removal of the 2-methoxypropyl protecting group in **6** have been separated chromato-

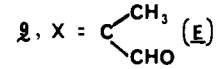


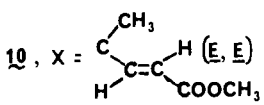


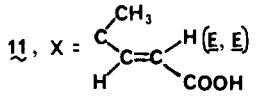
6, $R_1 = C(OCH_3)(CH_3)_2$, R_2 = H

7, R_1 = H, $R_2 = CH_3$

8, X = O

9, X =  (E)

10, X =  (E, E)

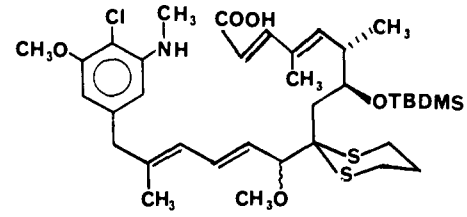
11, X =  (E, E)

graphically and individually carried through the synthesis; the more polar diol corresponds in relative stereochemistry to the maytansine series, whereas the less polar (slightly predominant) diol corresponds to the 10-epimaytansine series.

Reaction of **6** in THF–hexamethylphosphoramide (HMPA) (2:1) with sodium hydride (4 equiv) and methyl iodide (excess) at 0 °C for 3.5 h followed by brief stirring with THF–ether–1% aqueous HCl (1:1:1), extractive isolation, and chromatography on silica gel afforded the methoxy alcohols **7** (78% overall from dienal **5**), R_f 0.65 and 0.53 for **6** and **7** (ether, silica gel). The diastereomeric alcohols **7** could be resolved by high pressure liquid chromatography (HPLC, ratio of less polar to more polar 55:45) but not by thin layer chromatography. Oxidation of the primary alcohols **7** was effected using dimethyl sulfoxide–benzene (1:1) with 8 equiv of diethylcarbodiimide, 2 equiv of pyridine, and 1.95 equiv of trifluoroacetic acid for 8–10 h at 23 °C to give the aldehydes **8** (83% yield), R_f 0.53 and 0.60 for **7** and **8** (ether, silica gel). The elaboration of the aldehyde **8** to the enal **9** was accomplished by the method previously designed for this application.[5,9] The α-trimethylsilyl derivative of propionaldehyde *N-tert*-butylimine[9] was α-lithiated by reaction with *sec*-butyllithium in dry ether under argon at −78 °C (30 min) and then 0 °C (30 min) and the resulting reagent (1.3 equiv) was cooled to −78 °C and treated with 1 equiv of aldehyde **8.** After 16 h at −78 °C the mixture was quenched and stirred with 1 M 1:1 HOAc–NaOAc in aqueous acetone to give after extractive isolation **9** and a small amount of the isomeric *Z* enal. Isomerization of the *Z* enal in the mixture occurred upon stirring in CH_2Cl_2 with silica gel,[10] and pure **9** was isolated by chromatography on silica gel, yield 80%, R_f identically 0.60 for **8** and **9** (ether, silica gel).

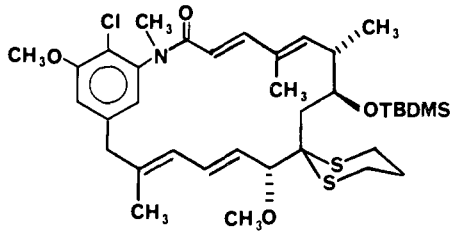
Chain extension of the *E* enal **9** to form the conjugated α,β-*E*-, τ,δ-*E*-unsaturated ester **10** was effected smoothly in 95% yield by reaction of **9** in THF with 2 equiv of the lithio derivative of dimethyl methoxycarbonylmethanephosphonate at 0 °C for 1 h and then 23 °C for 16 h. Hydrolysis of the ester **10** with a 5% solution of sodium hydroxide (CH_3OH–H_2O–THF (6:1:1.3) at 23 °C for 20 h furnished after chromatography on silica gel the corresponding acid **11** in pure condition (85% yield). Reaction of **11** with 4 equiv of lithium *n*-propyl mercaptide in HMPA (10 mL/g of **11**) at 0 °C for 8.5 h resulted in N-deprotection to give the amino acid **12** in 75–85% yield.

The stage was thus set for the formation of the macrocyclic system by cyclization of the amino acid **12.** After considerable



12

experimentation, an effective new lactamization process was developed for this step. The amino acid **12** was converted to the soluble tetra-*n*-butylammonium salt by reaction of 1 equiv of tetra-*n*-butylammonium hydroxide (azeotropically dried) in toluene. After azeotropic drying of the salt (using toluene), a solution of the salt in benzene was added gradually over 20 h by motor-driven syringe to a solution of excess mesitylenesulfonyl chloride and diisopropylethylamine in benzene and the components were allowed to react for an additional 3 h at 35 °C. After isolation and rough chromatography on silica gel the macrolactam **13** was obtained admixed with comparable amounts of the C-10 epimer (~65% yield). The two epimers were readily separated by preparative layer chromatography on silica gel using 1:1 ether–pentane, R_f 0.18 and 0.15 for **13** and the 10 epimer, respectively. The less polar epimer was known to be **13** by transformation to (±)-*N*-methylmaysenine (**2**) by a sequence of three unexceptional steps:[4c] (1) desilyla-



13

tion[11] using excess tetra-*n*-butylammonium fluoride in THF at 25 °C for 7–10 h; (2) carbamoylation of the resulting secondary hydroxyl at C-7 by successive reaction with excess *p*-nitrophenyl chloroformate–pyridine at 25 °C and excess ammonium hydroxide–*tert*-butyl alcohol at 25 °C; and (3) dithiane cleavage[4c] using excess mercuric chloride–calcium carbonate in 4:1 CH_3CN–H_2O at 23 °C for 8 h. Synthetic (±)-*N*-methylmaysenine (**2**) obtained in this way was shown to be spectroscopically and chromatographically identical with naturally derived *N*-methylmaysenine (vide infra). The C-10 epimer of **2** was synthesized from the C-10 epimer of **13** in a similar way, R_f 0.19 and 0.15 for **2** and 10-epi-**2**, respectively (ethyl acetate, silica gel).

An authentic sample of **2** was prepared from naturally derived maytansine[12] by a four-step sequence: (1) conversion to 9-*O*-methylmaytansine using 0.75 equiv of *p*-toluenesulfonic acid in methanol at 23 °C for 20 h;[2] (2) elimination of the 3-acyloxy group[3] using 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) in THF at 23 °C for 20 h to afford maysine 9-*O*-methyl ether; (3) hydrolysis of the 9-*O*-methyl ether in THF–5% aqueous HCl (2.5:1) at 23 °C for 1.5 h to form maysine;[3] and (4) removal of the 4,5-oxido oxygen using a large excess of chromous chloride[3] in acetic acid at 23 °C for 1 h.

Synthetic (±)-2 and naturally derived **2** were carefully compared chromatographically and spectroscopically. Identical TLC mobilities were observed using silica gel plates and 5 different solvent systems: ethyl acetate; THF–hexane 1:1; 5% isopropyl alcohol–CH_2Cl_2; CH_2Cl_2–CH_3OH–hexane–Et_2NH (75:75:100:2); and methyl acetate. Infrared, ultraviolet and NMR spectra were totally identical. Some characteristic ^1H NMR peaks for **2** are as follows (δ values): H-3 at 7.05 (d, J = 16 Hz); methyl signals at 3.80 (s, $ArOCH_3$), 3.20 and 3.15 (both s, 10-OCH_3 and *N*-CH_3), 1.52 (at C-14), 1.27 (at C-4), and 1.12 (*d*, J = 6 Hz, at C-6). The ultraviolet spectrum exhibited absorption maxima at 245 nm (ϵ 52 600) and 272 (31 200). Four characteristic infrared absorption bands were observed in the 1500–1800-cm^{-1} region at 1700, 1650, 1600, and 1580 cm^{-1}. The mass spectrum showed characteristic peaks at *m/e* 532, 530 ($M^+ + 2$, M^+), 512, 469, 454, and 434 along with other peaks at lower *m/e* values. Further confirmation of the synthetic product as (±)-**2** was obtained by conversion to the 9-*O*-methyl ether (CH_3OH, TsOH at 25 °C) and comparison with naturally derived *N*-methylmaysenine 9-*O*-methyl ether which revealed completely identical HPLC behavior and correspondence of mass spectra.

Now that our initial studies have established the feasibility of maytansenoid synthesis (and especially macrocyclic ring closure) by the approach described above, attention can now be turned to the synthesis of optically active maytansenoids and the control of stereochemistry at C-10. These and other problems, including the synthesis of maytansine itself, are the subject of current studies which will be reported in due course.[13,14]

References and Notes

(1) Submitted in remembrance of S. Morris Kupchan (1923–1976).
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(7) Satisfactory infrared, proton magnetic resonance, and mass spectral data were obtained using chromatographically homogeneous samples of each stable synthetic intermediate. All reactions involving basic or possibly air-sensitive components were conducted under an atmosphere of dry argon.
(8) This approach is based on the assumption (currently being tested) that both diastereomers are convertible to maytansenoids by adjustment of stereochemistry at C-10 *after* formation of the macrocyclic ring (which appears to be quite rigid).
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(10) Commercial silica gel for TLC chromatography containing calcium sulfate binder was used for this isomerization. The initial enal mixture (~9:1, *E*:*Z*) was completely transformed into the more stable *E* enal **9**. The relative chemical shifts in the *E* and *Z* enals were 9.24 and 10.15, respectively.
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(12) Maytansine was isolated in milligram amounts from an extract of *Maytenus serrata* kindly made available to us by Dr. John D. Douros of the National Cancer Institute and Dr. George L. Beemsterboer of the Monsanto Co. We thank both of these individuals and also Dr. Albert T. Sneden for their assistance and advice.
(13) It is a pleasure to express our thanks to a number of colleagues who provided valuable assistance in the prosecution of this work, in particular, A. V. Rama Rao, John Maher, Dale Boger, Janice Smith, and Homer Pearce.
(14) This research was assisted financially by a grant from the National Cancer Institute of the National Institutes of Health.

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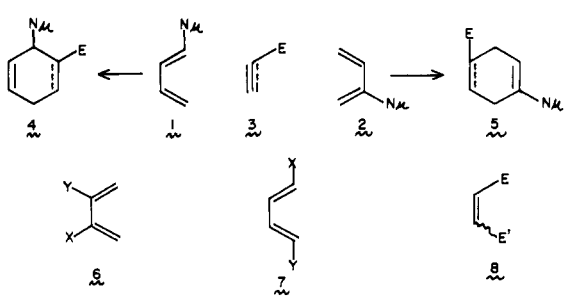
On the Use of *trans*-Methyl β-Nitroacrylate in Diels–Alder Reactions

Sir:

Precedent[1,2] and theory[3,4] tell us that cycloadditions of "nucleophilic" 1- and 2-substituted butadienes (cf. **1** and **2**) with "electrophilic" dienophiles of the type **3** (dotted lines refer to an acetylenic dienophile) will afford products of the type **4** and **5**, respectively. An important early finding in the Lewis acid catalyzed Diels–Alder reaction was its ability to provide greater regiochemical control with otherwise weakly directing groups (cf. alkyl) on the diene.[5,6]

Trost's studies have provided important new margins of regiochemical control, using 2,3-[7] (cf. **6**) and 1,4-diheterosubstituted[8] (cf. **7**) dienes in the presence or absence of Lewis acids. Valenta's studies have focused on the use of such catalysis to control the orientational dominance of dienophiles of the type **8**, where E and E′ are both electron withdrawing.[9–11] Often the catalyst, for steric or other reasons, is able to dramatically and usefully effect the relative directing po-



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