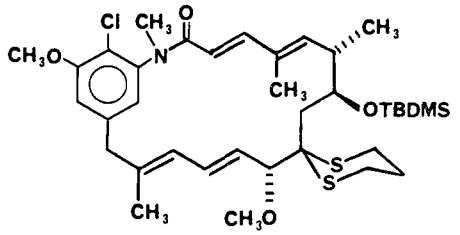

13

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]

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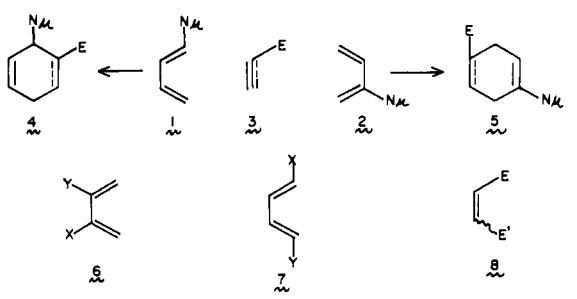
On the Use of *trans*-Methyl β-Nitroacrylate in Diels–Alder Reactions

Sir:

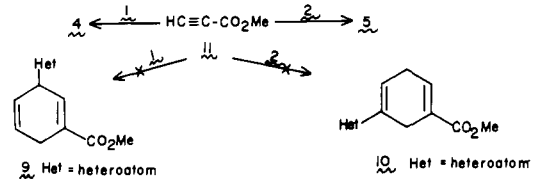
Precedent[1,2] and theory[3,4] tell us that cycloadditions of "nucleophilic" 1- and 2-substituted butadienes (cf. **1** and **2**) with "electrophilic" dienophiles of the type **3** (dotted lines refer to an acetylenic dienophile) will afford products of the type **4** and **5**, respectively. An important 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-



tency of E and E′ (e.g., unsymmetrical quinones[9,10] and methyl β-formylacrylate).[11]

We sought to find a dienophile which would provide a regiochemical pattern opposite to that available from Diels–Alder reactions of acetylenic dienophiles with nucleophilic dienes. In this exploratory phase, we concentrated on the case of E = carbomethoxyl. Thus, our general lines of inquiry could be sharpened to that of seeking simple routes to generic systems **9** and **10.** The specific reasons for our seeking this smooth access to such compounds will be clarified through future publications in this series.



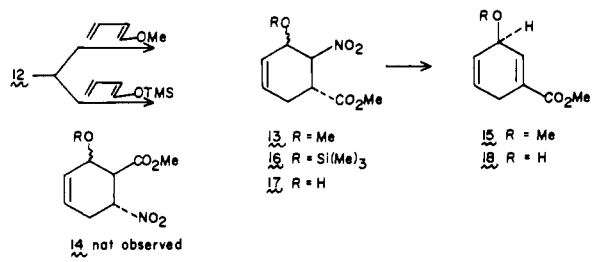
9, Het = heteroatom **10**, Het = heteroatom

As will be shown below, the specific dienophile which we have used to solve this problem is the readily available *trans*-methyl β-nitroacrylate (**12**).[12,13] The dienophilicity of **12** was already apparent from the work of Just.[14,15] However, those studies were conducted with symmetrical dienes. Thus, they did not address what was for us the most critical issue, i.e., that of regiochemistry. The elegant route to α-methylenebutyrolactones due to McMurry[16] demonstrates that a nitro group predominates over an ester in controlling the direction of Michael addition. We hoped that this preponderance might also be exhibited in Diels–Alder reactions of **12** with **1** and **2.** Facile β-elimination of nitrous acid[14,16] would complete the scheme. Our results are summarized below.

Cycloaddition of **12** with *trans*-1-methoxybutadiene (2 equiv) occurred at room temperature in benzene. After 26 h, there was isolated by column chromatography, a 93% yield of an essentially 1:1 mixture of stereoisomers corresponding to **13.** We could find no regioisomers corresponding to **14.** Treatment of this mixture with 1 equiv of diazabicycloundecene (DBU) afforded 30–40% yields of pure **15** after chromatography: δ ($CDCl_3$) 2.90 (2 H, m), 3.29 (3 H, s), 3.73 (3 H, s), 4.50 (1 H, m), 5.90 (2 H, m), 6.92 (1 H, m) ppm.

Under similar conditions, reaction of **12** with *trans*-1-trimethylsilyloxy-1,3-butadiene[17] afforded (quantitatively) the stereoisomeric adducts, **16.** Treatment of **16** with the two-phase system ether–10% aqueous H_2SO_4 followed by chromatography afforded the stereoisomeric hydroxy adducts **17**[18a] in 78% yield. Treatment of this mixture with 1.1 equiv of K_2CO_3–MeOH at room temperature for 45 min afforded a 68% isolated yield of the labile dihydrobenzoate **18:**[18a] δ ($CDCl_3$) 2.20 (1 H, s, exchanges with D_2O), 2.87 (2 H, m), 3.75 (3 H, s), 4.66 (1 H, m), 5.90 (2 H, s), 6.93 (1 H, br s) ppm.

From these results we surmise that the nitro group exercises complete regiochemical control with the highly "nucleophilic" 1-oxygenated butadienes. Unfortunately, there is essentially no corresponding "endo" stereoselectivity. Nonetheless, one can effect β-elimination of the nitro group (in the presence of a potentially serious β-elimination of the oxygen function) under sufficiently mild conditions to afford the highly labile,



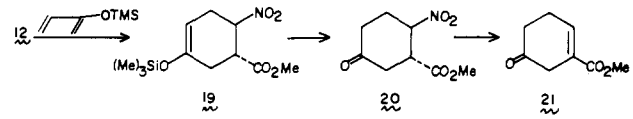
13, R = Me; **16**, R = Si(Me)$_3$; **17**, R = H

14 not observed

15, R = Me; **18**, R = H

new, prebenzenoid systems **15** and **18** in reasonable overall yield.

Reaction of **12** with 2-trimethylsilyloxy-1,3-butadiene[17,19] occurs in benzene at room temperature, giving after 42 h a quantitative yield of **19.**[18a] Treatment of **19** with aqueous acetic acid afforded a 72% yield of analytically pure *trans*-4-nitro-3-carbomethoxycyclohexanone (**20**),[18a,b] mp 94–95 °C. Reaction of **20** with DBU (room temperature, THF) affords a 99% yield of essentially pure cyclohexenone **21:**[18a,20] δ ($CDCl_3$) 2.28 (4 H, m), 3.15 (2 H, m), 3.80 (3 H, s), 7.20 (1 H, m).

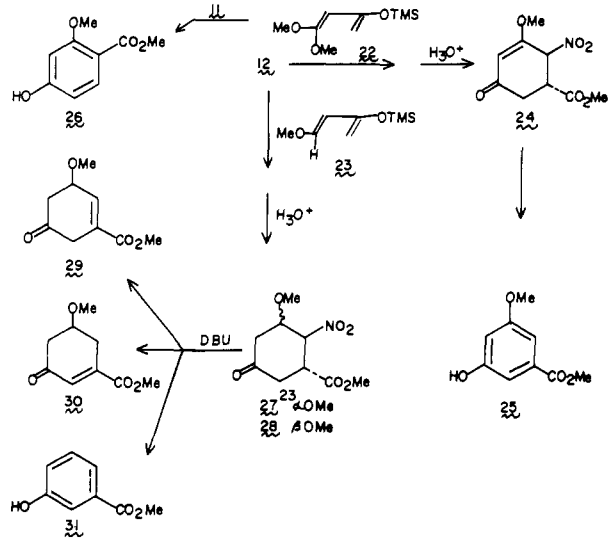


19 **20** **21**

Fascinating functionality patterns are readily achieved by Diels–Alder reactions of **12** with dienes **22**[21] and **23.**[22] Cycloaddition of **12** with **22** was conducted at 0 °C → room temperature for 1 h. The adduct was treated directly with 4:1 THF–0.1 N HCl to afford an 82% yield of the crystalline **24,**[18] mp 102–105 °C dec. Treatment of **24** with DBU–THF afforded a 99% yield of resorcinol derivative **25,** mp 92.5–93.5 °C.[18] It will be recalled[21] that cycloaddition of the same **22** with **11** afforded a high yield of the isomeric product **26.** Thus, both trisubstituted aromatic patterns are now readily available through simple Diels–Alder chemistry.

Similarly, reaction of **12** with **23** is exothermic at room temperature. Treatment of the resulting adduct with aqueous acetic acid followed by fractional crystallization from hexane–ethyl acetate afforded a 48% yield of the homogeneous **27,**[18] mp 110–111 °C.[23] The mother liquors contain more of **27** as well as its stereoisomer, **28.** Unfortunately, **28** could not be obtained in homogeneous form.

Treatment of **27** with DBU afforded variable mixtures of **29,**[18a] **30,** and some phenol, **31.** Attempted chromatographic separation of **29** and **30** on silica gel led to further conversion of **29** → **30**[18a] and the latter was isolated in 38% yield.[24] Compound **29** was not obtained in pure form.



26 **12** **22** **24** **23** **29** **30** **27** **28** **25** **31**

It would seem that the ability of the nitro group in **12** to exercise regiochemical control in [4 + 2] reactions with dienes of the type **1** and **2** provides comfortable access to hitherto difficultly available substitution patterns. The power of the method is enhanced when one considers permutations in which the nitro group is retained or eliminated. The applications of this "umpolung" of Diels–Alder reactivity[25] will be the subject of future disclosures.

Acknowledgments. This research was supported by P.H.S.

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(24) Compound **30** is chromatographically somewhat unstable with respect to β-elimination of methanol and formation of phenol **31**. A trace of **31** is suggested in NMR spectrum of **30**.
(25) Several previous strategies, using Diels–Alder reactions together with other manipulations to afford "meta" type cyclohexenes are seen in the studies of Büchi,[26] Trost,[27] Cohen,[26] and Valenta.[11] The research described herein provides a direct solution to "meta" type cyclohexadienes.
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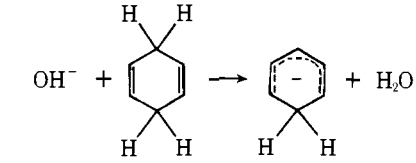
Gas Phase Oxidation and Reduction Reactions with $C_6H_7^-$, HNO^-, and HO_2^-

Sir:

Although gas phase proton transfer reactions have been extensively studied,[1] there have been few investigations of hydride transfer between ions and neutral molecules in the gas phase, primarily because of a lack of methods for the synthesis of hydride donors.[2] We wish to report that the cyclohexadiene anion (I) readily transfers a hydride ion to a number of substrates, both organic and inorganic, and so provides a convenient entry into extensive new fields of gas phase ion–molecule chemistry.

We produce hydroxide or amide ions in the ionization region of a flowing afterglow system[3,4] and add 1,4-cyclohexadiene 10 cm downstream. The anion I is formed by rapid proton transfer (eq 1). Other reactants may be added through fixed



$$OH^- + \text{(cyclohexadiene)} \rightarrow \text{(cyclohexadienyl anion)} + H_2O \quad (1)$$

I

or movable inlets further downstream before the ions are sampled and analyzed by a quadrupole mass filter.[5]

Reaction of benzaldehyde (mol wt 106) with I results in rapid formation of a new ion of m/e 107. We formulate this species as the anion of benzyl alcohol generated by nucleophilic hydride addition to the carbonyl group:

$$I + C_6H_5CHO \rightarrow C_6H_5CH_2O^- + C_6H_6 \quad (2)$$

Acrolein (mol wt 56) is also reduced by I to an ion of m/e 57:

$$I + CH_2{=}CHCHO \rightarrow C_3H_5O^- + C_6H_6 \quad (3)$$

Cyclohexadiene anion also reacts rapidly with nitric oxide to give HNO^-,

$$I + NO \rightarrow HNO^- + C_6H_6 \quad (4)$$

which in some ways is an even more useful hydride donor. For example, HNO^- reduces nitrous oxide to HN_2O^- and carbon dioxide to formate ion.

$$HNO^- + N_2O \rightarrow HN_2O^- + NO \quad (5)$$

$$HNO^- + CO_2 \rightarrow HCOO^- + NO \quad (6)$$

I, on the other hand, does not react with nitrous oxide and only the addition product $C_6H_7CO_2^-$ is observed upon reaction with carbon dioxide. HNO^- also reduces benzaldehyde and acrolein, in the latter case more cleanly than does I, whose reaction is complicated by a competing addition reaction. HNO^- is also known[2] to hydride transfer to R_3B and can thus serve as a precursor of gas phase borohydride ions.

Hydride transfer from I to oxygen occurs rapidly to form the hydroperoxide ion,

$$I + O_2 \rightarrow HOO^- + C_6H_6 \quad (7)$$

a potent oxidizing agent in the gas phase just as in solution. Benzaldehyde is oxidized to the benzoate ion by HO_2^-, and carbon dioxide, carbon monoxide, and nitric oxide are also readily oxidized.

$$HO_2^- + C_6H_5CHO \rightarrow C_6H_5COO^- + H_2O \quad (8)$$

$$HO_2^- + CO_2 \rightarrow CO_3^- + OH \quad (9)$$

$$HO_2^- + CO \rightarrow OH^- + CO_2 \quad (10)$$

$$HO_2^- + NO \rightarrow NO_2^- + OH \quad (11)$$

All three anions, I, HNO^-, and HO_2^-, can serve as bases in the gas phase, so that proton abstraction from substrates with relatively acidic protons can be a complicating factor.[6] Nevertheless, these anions, and many others which they can be used to create, promise to be of great value for the study of gas phase ion–molecule reactions.

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