Table I. Mass Spectral Characteristics of $[C_4H_4O]^{+\cdot}$ Ions

precursor molecule	metastable peaks[a] loss of CO $T_{0.5}$[c]	T_{av}[c]	rel abundances m/z 40	m/z 42	partial 70-eV collisional activation spectra[b] (major peaks) m/z 39	m/z 40	m/z 42
furan	17	87	100	19	100	17	12
cis/trans-crotonic acid	25	65	100	5	100	49	24
3-butenoic acid	25	65	100	5	100	53	26
cyclopropanecarboxylic acid	25	65	100	5	100	49	24
methyl crotonate	25	65	100	5	100	67	25
cyclohexen-2-one	33[d]	68	100	6.5	100	48	22
vinylketene (II)	22	60	100	5	100	45	21

[a] Measured with an AEI-GEC MS902S mass spectrometer under conditions of good energy resolution.[8] [b] Measured with a VG-Micromass ZAB 2F mass spectrometer. Acceleration voltage, 8000 V; collision gas, He. Peaks arising from unimolecular processes were separated from collision-induced processes by means of a voltage (−320 V) applied to the collision gas cell. Further experimental details are given elsewhere.[9] [c] Kinetic energy releases (millielectronvolts) evaluated from the metastable peak widths at half height ($T_{0.5}$) and T_{av} from the distribution of released energies.[10] [d] The larger energy releases observed for this compound are due to a contribution from another $[C_4H_4O]^{+\cdot}$ ion, [cyclobutenone]$^{+\cdot}$ ($T_{0.5}$ = 38 meV, T_{av} = 77 meV, which can be generated by loss of CO from 4-cyclopentene-1,3-dione).

27, $[C_2H_3]^+$ (52%); m/z 26, $[C_2H_2]^{+\cdot}$ (48%); m/z 25 $[C_2H]^+$ (9%). In marked contrast, the 70-eV mass spectrum of I, measured in an instrument wholly at room temperature,[12] showed an intense molecular ion for I, m/z 96, and major peaks at m/z 67, $[C_4H_3O]^+$, and m/e 29, $[C_2H_5]^+$, in addition to those at m/z 68, 42, 40, 39, 27, and 26.

The low energy region of the He(I) photoelectron (PE) spectrum of I, measured at room temperature, contained a diffuse peak centered at 8.67 eV. This disappeared when the sample inlet system was heated to ~100 °C, to be replaced by a sharp peak at a lower energy, 8.29 ± 0.05 eV, and another at 10.23 ± 0.05 eV. The AE of m/e 68, $[C_4H_4O]^{+\cdot}$, measured with energy selected electrons and now using a pyrolytic gas inlet system[12] (T range, 350–650 °C) was 8.34 ± 0.05 eV. Within experimental error, this is the same value as the ionization energy (IE) obtained from the PE spectrum; this result further supports the conclusion that a *molecular* species II, C_4H_4O, is being thermally generated from I. The magnitude of the IE for this C_4H_4O molecule is consistent with that for a conjugated ketene (cf. IE (ketene) = 9.6 eV,[7] IE (phenylketene) = 8.17 eV[13]). Furthermore, IE values for other C_4H_4O isomers are significantly higher, e.g., IE (furan) = 8.88 eV,[7] IE (methylcyclopropenone) = 9.28 eV,[6] IE (cyclobutenone) (estimated value) = 9.3 eV,[6] IE (but-2-ynal and but-3-yn-2-one) = 10.28 eV (HE(I) PE spectra, this work). These data effectively rule out C_4H_4O structures for II other than vinylketene and possibly its double-bond isomer buta-1,2-dienone. ΔH_f for vinylketene molecular ion would be 195 ± 1 kcal mol^{-1} (ΔH_f (vinylketene) = +4 kcal mol^{-1}, estimated from ΔH_f (CH_2CO) = −14.6 kcal mol^{-1},[7] ΔH_f ($CH_2{=}C{=}CH_2$) = +45.9 kcal mol^{-1},[7] ΔH_f ($CH_2{=}CHCH{=}C{=}CH_2$ = +64.9 kcal mol^{-1} [14]) in agreement with ΔH_f ($[C_4H_4O]^{+\cdot}$) from cyclohexen-2-one,[6] 194 ± 1 kcal mol^{-1}. Note the close similarity between the mass spectral characteristics for $[C_4H_4O]^{+\cdot}$ derived from I, from cyclohexen-2-one, and from other species (see Table I) whose fragmentations have been proposed to generate [vinylketene]$^{+\cdot}$. The above estimated value for ΔH_f (vinylketene) is supported by the AE for $[C_3H_4]^{+\cdot}$ derived from II, 10.36 ± 0.05 eV. This value combined with ΔH_f (CO) = −26.4 kcal mol^{-1} [7] and ΔH_f ($[CH_2{=}C{=}CH_2]^{+\cdot}$) = 269 kcal mol^{-1} [7] also gives ΔH_f (C_4H_4O) = +4 kcal mol^{-1}, in good agreement with the above estimate. Similarly, comparing ΔH_f ($CH_3CH{=}C{=}C{=}CH_2$) = +73.2 kcal mol^{-1} [14] with the ΔH_f data for ketene and allene, leads to ΔH_f (buta-1,2-dienone) = +13 kcal mol^{-1}. Such a heat of formation makes this molecular species quite incompatible with the above observations and so II can indeed confidently be identified as vinylketene. It is a relatively stable species in gas phase; for example, although samples prepared in the heated MS902 inlet system initially gave a mass spectrum characteristic of I, ions at m/z 96, 67, etc., quickly disappeared leaving a time-invarient mass spectrum[15] of II as reported above.

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Stereocontrolled Synthesis of the Prelog–Djerassi Lactone

Sir:

The Prelog–Djerassi lactone (**1**) is a key degradation product of the antibiotic methymycin,[1] which retains the configuration[2] of the four chiral centers present in the segment comprising

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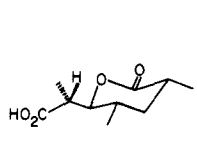
C-1 through C-7 of the aglycone methynolide (**2**). The lactonic



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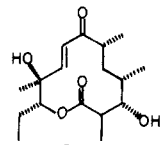

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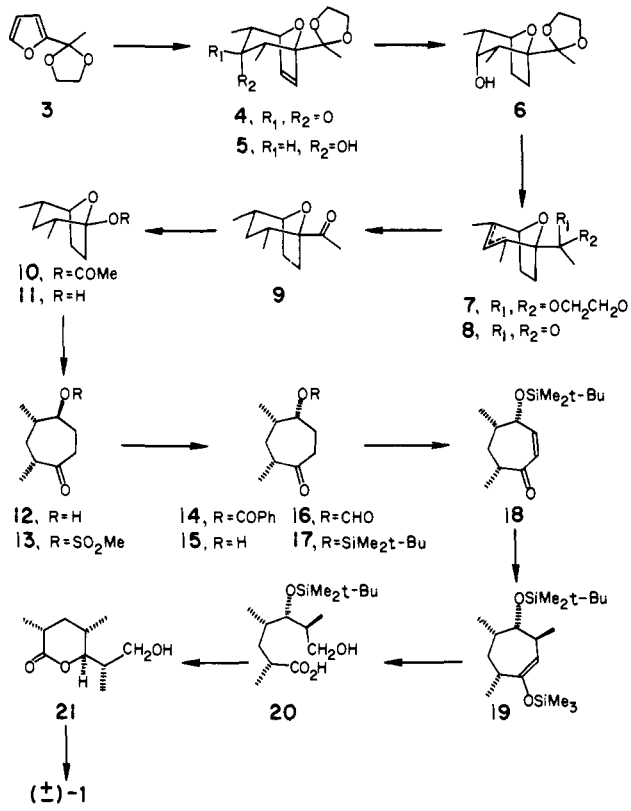
acid **1** was a pivotal intermediate in Masamune's synthesis of methymycin,[3] and our strategy for elaboration of this macrolide likewise calls for homologation of **1** and connection with a second segment[4] constituting C-9 through C-11 of the seco acid. We report a novel and fully stereocontrolled synthesis of (±)-**1** which has, as a central feature, construction of an 8-oxabicyclo[3.2.1]octane system incorporating C-4 and C-6 methyl groups of methynolide directly and in the correct orientation.

2-Acetylfuran was converted to its ethylene ketal **3** (85%; $CH(OMe)_3$, $(CH_2OH)_2$, *p*-TsOH, 25 °C, 16 h), which was treated with 2,4-dibromopentan-3-one in the presence of zinc/copper couple (glyme, 0–25 °C, 16 h) to give a single adduct **4** (mp 69.5–70.5 °C; ν_{max} 1703 cm^{-1}; NMR δ 0.97 (3 H, d, J = 7 Hz), 1.07 (3 H, d, J = 7 Hz), 1.40 (3 H, s), 2.84 (2 H, m), 4.03 (4 H, m), 4.96 (1 H, d, J = 4.5 Hz), 6.24 (2 H, s)) in 53% yield.[5] The spectral data of **4** indicate that, in conformity with similar cycloadditions of the oxoallyl cation,[6] reaction occurs with high stereoselectivity leading to a cis diequatorial disposition of the two methyl substituents. Reduction of **4** ($AlH(i\text{-}Bu)_2$, THF, 0 °C, 3 h) gave an alcohol (85%; mp 73–74 °C; ν_{max} 3450 cm^{-1}) which, from its NMR spectrum (δ 3.68 (1 H, d of d, J = 5, 5 Hz)), was the expected endo



product **5**.[7] Hydrogenation of this substance (10% Pd/C, 95% EtOH) afforded the dihydro derivative **6** (mp 106–108 °C) in quantitative yield, and exposure of the latter to methanesulfonyl chloride in pyridine (25 °C, 3 days) gave an oily mixture of two olefins (**7**) in 78% yield. The ketal function was then hydrolyzed (AcOH–THF–H_2O in the ratio 2:1:1, 80 °C, 3 h), furnishing a pair of olefinic ketones (**8**) (90%; ν_{max} 1718 cm^{-1}; NMR δ 2.27 (3 H, s)) which was hydrogenated (10% Pd/C, absolute EtOH) exclusively from the exo face to give a single saturated ketone (**9**) (96%; ν_{max} 1710 cm^{-1}; NMR δ 0.71 (3 H, d, J = 7 Hz), 0.79 (3 H, d, J = 7 Hz), 2.24 (3 H, s), 4.16 (1 H, m)).[8]

The acetyl function of **9** serves to actuate fission of the ether bridge in this framework, which was found to be exceptionally resistant to cleavage by acid catalysis. Thus, Baeyer–Villiger oxidation of **9** (*m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 25 °C, 4 days) yielded acetate **10** which, upon saponification (K_2CO_3 in MeOH–H_2O (5:2)), led to cycloheptanone **12** (60% from **9**; mp 34–36 °C; ν_{max} 3380, 1705 cm^{-1}; NMR δ 4.15 (1 H, m)), presumably via the bicyclic hemiketal **11**. The relative configuration of the hydroxyl group in **12** is epimeric with the natural orientation of the hydroxyl at C-3 of **2**, and reversal of this configuration was undertaken as the next task. This was achieved by conversion of **12** to its mesylate **13** (97%) with methanesulfonyl chloride (pyridine, 25 °C, 16 h), followed by treatment with potassium benzoate in the presence of 18-crown-6 (CH_3CN–Me_2SO (4:3), 95 °C, 20 h),[9] to yield benzoate **14** (85%; ν_{max} 1705, 1700 cm^{-1}; NMR δ 5.36 (1 H, m)). Saponification of **14** (K_2CO_3, MeOH–H_2O (2:1), 75 °C, 4 h) provided **15** as an oil (89%; ν_{max} 3380, 1700 cm^{-1}; NMR δ 0.91 (3 H, d, J = 7 Hz), 1.10 (3 H, d, J = 6 Hz), 3.66 (1 H, exchanged with D_2O), 4.13 (1 H, m)). An alternative and more convenient inversion procedure for large-scale preparation of **15** entailed treatment of **13** with tetra-*n*-butylammonium formate (Me_2CO–HMPA, 65 °C),[10] followed by saponification (K_2CO_3, MeOH–H_2O (8:3), 25 °C, 4 h) of the resulting formate ester **16**; this gave **15** in 77% yield.

For subsequent operations it was necessary to protect the hydroxyl function of **15**, which was accomplished by conversion (*tert*-butyldimethylchlorosilane, imidazole, DMF, 25 °C, 20 h)[11] to silyl ether **17** (97%). This masking group actually serves a second purpose in our scheme since its steric bulk blockades the α face of the cycloheptanone and steers the entering methyl substituent at C-6 toward the β side of this ring. First, however, an enone function was introduced into **17** by deprotonation with lithium 2,2,6,6-tetramethylpiperidide[12] (THF, −78 °C, 25 min), followed by quenching with phenylselenyl chloride (THF, −78 °C for 30 min and then 0 °C for 1 h) and oxidation (30% H_2O_2 in AcOH, 0–25 °C). This gave cycloheptenone **18**[13] (57%; ν_{max} 1670, 1606 cm^{-1}; NMR δ 0.07 (6 H, s), 0.91 (9 H, s), 0.98 (3 H, d, J = 7 Hz), 1.10 (3 H, d, J = 7 Hz), 4.67 (1 H, m), 5.95 (1 H, d of d, J = 2, 12 Hz), 6.43 (1 H, d of d, J = 4, 12 Hz)), together with trace quantities of the alternate, endo and exo α,β-unsaturated ketones.

Insertion of the remaining methyl substituent into this framework was accomplished with lithium dimethylcuprate (ether, 0 °C), and the enolate resulting from conjugate addition was trapped with trimethylsilyl chloride as the enol ether **19**.[14] Without purification, this labile substance was ozonized (CH_2Cl_2–MeOH, −78 °C), and the crude product was reduced with sodium borohydride to give hydroxy ester **20**.[15] Acidic removal of the silyl ether protecting group (15% HCl, THF, 60 °C) resulted in concomitant lactonization to **21**, which was oxidized with Jones reagent to (±)-**1** (12% from **18**; mp 110–113 °C), identical by melting point, mixture melting point, IR, NMR, and mass spectral comparison with an authentic sample of racemic Prelog–Djerassi lactone.[16] This route to **1** not only affords an alternative strategy for the synthesis of methylnolide (**2**) but also opens prospective approaches to macrolide antibiotics (picromycin, narbomycin, erythromycin) which contain segments similar in structure and configuration to the C-1–C-7 fragment of **2**.[17]

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(18) National Institutes of Health Research Career Development Awardee, 1976–1981.

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Dehydrohalogenation by Complex Base. Preferential Loss of "Poorer" Halogen Leaving Groups

Sir:

In olefin formation by base-promoted dehydrohalogenation, an order of leaving group reactivity of I > Br > Cl ≫ F has been observed on several occassions.[1,2] This is the normal trend expected for the operation of a leaving group "element effect"[3] in a concerted E2 mechanism. We report a reversal of this leaving group ordering for syn eliminations from *trans*-1,2-dihalocycloalklanes promoted by "complex base".

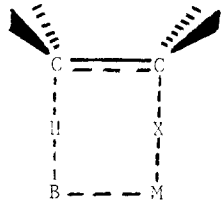
Caubere[4] has reported a surprising propensity for a mixture of $NaNH_2$–NaO-*t*-Bu, "complex base," to induce syn eliminations from *trans*-1,2-dibromocycloalkanes (C_5–C_7). Thus, when treated with $NaNH_2$–NaO-*t*-Bu in THF at room temperature, *trans*-1,2-dibromocyclohexane yielded 60% 1-bromocyclohexene and 36% cyclohexene. Under the same conditions, neither $NaNH_2$ nor NaO-*t*-Bu gave significant amounts of 1-bromocyclohexene. This method is now the preferred synthetic route to several 1-bromocycloalkenes.

In an attempt to gain mechanistic insight into this reaction, we have investigated complex base promoted eliminations from *trans*-1,2-dihalocyclohexanes which contain two different halogen atoms. Reaction of *trans*-1-bromo-2-chlorocyclohexane with $NaNH_2$–NaO-*t*-Bu in THF at room temperature for 24 h yielded 52–55% 1-bromocyclohexene and 30–31% 1-chlorocyclohexene.[5,6] Dehydrohalogenation involving the "poorer" leaving group is preferred. This tendency was further accentuated in reactions of *trans*-1-bromo-2-fluorocyclohexane and *trans*-1-chloro-2-fluorocyclohexane with complex base under the same conditions.[5,6] The former dihalide gave an 85% yield of 1-bromocyclohexene and the latter an 85% yield of 1-chlorocyclohexene. No 1-fluorocyclohexene was detected in either elimination. Thus, dehydrofluorination occurs in preference to dehydrochlorination or dehydrobromination in these complex base promoted syn eliminations.[7] This is particularly striking in view of the forcing conditions required to induce dehydrofluorination from alkyl fluorides.[1,9,10]

Reaction of *trans*-1-bromo-2-chlorocyclopentane with $NaNH_2$–NaO-*t*-Bu in THF at room temperature for 20 h produced 50% 1-bromocyclopentene and 38% 1-chlorocyclopentene. Similarly, treatment of *trans*-1-chloro-2-bromoacenaphthene with complex base in THF at 0 °C[11] for 5 h yielded 54% 1-bromoacenaphthylene and 42% 1-chloroacenaphthylene. These results demonstrate that the preference for syn dehydrochlorination over syn dehydrobromination with complex base is not limited to six-membered-ring dihalides.

The preferential loss of "poorer" halogen leaving groups in complex base promoted eliminations is confined to reactions with syn stereochemistry. Treatment of 1-bromo-1-chlorocyclohexane and *cis*-1-bromo-2-chlorocyclohexane with $NaNH_2$–NaO-*t*-Bu in THF at room temperature for 16 and 12 h,[5] respectively, produced 99% yields of 1-chlorocyclohexene. Only traces of 1-bromocyclohexene were detected. Therefore, complex base promoted anti eliminations from 1,1- and *cis*-1,2-dihalocyclohexanes exhibit the same preference for dehydrobromination over dehydrochlorination noted with more ordinary base-solvent combinations.[12] This result suggests an E2 mechanism for dehydrohalogenations involving complex base, but with some special interactions for syn eliminations.

The facilitation of concerted syn elimination by ion-paired bases has been explained using the cyclic transition state **1**.[13,14]



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In this transition state, the metal cation, M, simultaneously coordinates with the base, B, and the leaving group, X. Our current observations may be readily rationalized if, for syn eliminations promoted by complex base, the strength of interaction between X and M becomes the dominant leaving group property rather than the customary preeminence of the C–X bond strength. Because of its high electronegativity favoring strong interactions with M, fluoro would be the preferred halogen leaving group. Similarly, the chloro leaving group should be removed in preference to bromo.

Further aspects of the mechanistic and synthetic features of complex base promoted 1,2 eliminations are in progress.

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