General Procedure for the Preparation of Vinyl Spiro Epoxides. 1-[(Methylthio)methyl]cyclohex-2-en-1-ol (7). To *n*-butyllithium (28.6 mL, 1.75 M in hexane, 50 mmol) chilled in an ice water bath was added TMEDA (5.8 g, 50 mmol). The mixture was warmed to room temperature and allowed to stir for 30 min. The mixture was cooled to 0 °C, and dimethyl sulfide[7] (3.13 g, 50.0 mmol) was added. The resulting pale yellow solution was stirred for 3.5 h at room temperature and cooled to −78 °C (dry ice–2-propanol), and a solution of 2-cyclohexen-1-one (4.85 g, 50 mmol) in THF (30 mL) was added over 5 min. The mixture was warmed to room temperature and cast into ether (150 mL) and saturated aqueous NH_4Cl (150 mL). The organic phase was separated, washed with water (150 mL), dried (Na_2SO_4), and concentrated in vacuo to provide a viscous yellow liquid. The crude product was purified by distillation, bp 65–68 °C (0.007 mm), to provide 6.7 g, 88%, of 1-[(methylthio)methyl]cyclohex-2-en-1-ol (7) as a colorless, viscous liquid. ^1H NMR (250 MHz): δ 5.85 (ddd, J = 10, 4, 3.15 Hz, 1 H), 5.66 (dddd, J = 9.5, 2.4, 2.0, 0.77 Hz, 1 H), 2.75 (d, J = 13.4 Hz, 1 H), 2.67 (d, J = 13.4 Hz, 1 H), 2.50 (br s, 1 H), 2.20 (s, 3 H), 2.09–1.95 (2 H), 1.85–1.57 (4 H). EI/MS (70 eV): 158 (M^+, 6.65), 141 (32.3), 95 (base). IR (neat): 3470 (br), 3050, 2950, 2855, 1645, 1435, 1220, 1185, 1055, 1000, 965 (br), 740 cm^{-1}.

1-[(Dimethylsulfonio)methyl]cyclohex-2-en-1-ol (8). To a solution of allylic alcohol 7 (3.16 g, 20 mmol) in dry acetone (10 mL) was added methyl iodide (5.67 g, 40 mmol). The mixture was allowed to stir at room temperature overnight and then concentrated in vacuo to provide 6.0 g, 100%, of the sulfonium salt 8 as a white solid, mp 155 °C dec, that was used without further purification.

8-Oxaspiro[5.2]oct-2-ene (6). To a suspension of the sulfonium salt 8 (6.0 g, 20 mmol) in 250 mL of THF was added 2.9 g (25.9 mmol) of freshly sublimed KO-*t*-Bu. The mixture was allowed to stir at room temperature for 4 h, quenched with saturated aqueous $NaHCO_3$ (50 mL), and was cast into ether (250 mL). The aqueous phase was separated and extracted with ether (4 × 100 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ (0.5 L) and brine (0.5 L) and dried ($MgSO_4$, K_2CO_3). The solvent was removed by distillation at atmospheric pressure, and the residue was purified by distillation, bp 70–72 °C (0.37 mm), to provide 2.0 g, 91%, of 6 as a colorless liquid. ^1H NMR (250 MHz, $CDCl_3$): δ 6.12 (ddd, J = 10.07, 3.97, 3.66 Hz, 1 H), 5.25 (br d, J = 10.07 Hz, 1 H), 2.84 (d, J = 4.88 Hz, 1 H), 2.79 (d, J = 4.88 Hz, 1 H), 2.3–1.5 (6 H). EI/MS (70 eV): 110 (M^+, 83), 93 (51), 79 (base). IR (neat): 3080, 3020, 1460, 950, 810, 760 cm^{-1}. MS: M^+ calcd for $C_7H_{10}O$ 110.073160, M^+ found 110.07320.

Vinyl Spiro Epoxides 10. ^1H NMR (250 MHz, C_6D_6): δ 5.34 (m, 1 H), 3.61 (dd, J = 10.15, 0.45 Hz, 1 H), 3.42 (d, J = 10.15 Hz, 1 H), 2.15–1.62 (4 H), 1.73 (m, 3 H). EI/MS (70 eV): 110 (M^+, 22), 95 (6), 81 (base), 79 (61), 77 (24), 67 (11), 53 (35), 40 (37). IR (neat): 3040, 2995, 1460, 910, 860, 740 cm^{-1}.

Vinyl Spiro Epoxides 12 and 13. ^1H NMR (250 MHz, C_6D_6): δ 5.64 (m, 0.18 H), 5.53 (m, 0.82 H), 4.69 (m, 2 H), 2.78 (d, J = 4.74 Hz, 0.18 H), 2.59 (dd, J = 5.22, 1.73 Hz, 0.82 H), 2.33 (d, J = 4.74 Hz, 0.18 H), 2.27 (d, J = 5.22 Hz, 0.82 H), 2.1–1.3 (5 H), 1.54 (br s, 3 H), 1.47 (m, 3 H). EI/MS (70 eV): 164 (M^+, 13), 149 (44), 133 (16), 123 (58), 119 (79), 107 (91), 91 (base), 79 (49), 67 (21). IR (neat): 2945, 1685 (w), 1650, 1383, 1340, 1068, 945, 900, 842, 810 cm^{-1}.

Vinyl Spiro Epoxide 15. ^1H NMR (250 MHz, C_6D_6): δ 4.93 (m, 1 H), 2.50 (d, J = 5.24 Hz, 1 H), 2.32 (d, J = 5.24 Hz, 1 H), 1.51 (d, J = 0.84 Hz, 3 H), 1.85–1.2 (6 H), 1.08 (d, J = 7.55 Hz, 3 H), 0.94 (d, J = 7.55 Hz, 3 H). EI/MS (70 eV): 166 (M^+, 11), 149 (9.3), 137 (27), 121 (20), 105 (34), 93 (73), 81 (base), 69 (34), 55 (25), 43 (62). IR (neat): 2990, 2900, 2870, 1470, 1375, 1205, 1170, 1068, 720 cm^{-1}.

Vinyl Spiro Epoxide 17. ^1H NMR (250 MHz, C_6D_6): δ 5.54 (br s, 1 H), 3.45 (ab q, J = 13.26, 10.78 Hz, 2 H), 1.59 (br s, 3 H), 0.90 (br s, 6 H), 1.8–1.2 (4 H). EI/MS (70 eV): 152 (M^+, 11), 151 (11), 123 (39), 109 (18), 107 (23), 95 (30), 91 (21), 81 (35), 69 (base), 55 (22). IR (neat): 2990 (br), 2890, 2850, 1680 (w), 1460, 1375, 1285, 1195, 1140, 1070, 1040, 915, 830 cm^{-1}.

Vinyl Spiro Epoxide 19. ^1H NMR (250 mHz, C_6D_6): δ 4.97 (br s, 1 H), 4.69 (br s, 2 H), 3.65 (d q, J = 3.65, 1.67 Hz, 2 H), 3.50 (t, J = 8.48 Hz, 1 H), 3.39 (t, J = 5.02 Hz, 1 H), 3.14 (s, 3 H), 2.53 (br s, 2 H), 2.16–1.86 (4 H), 1.70–0.55 (16 H), 0.89 (s, 3 H), 0.87 (s, 3 H). EI/MS (70 eV): 390 (M^+, 0.32), 377 (0.41), 312 (0.28), 300 (0.96), 147 (4), 133 (4), 119 (5), 105 (9), 89 (base), 79 (7), 59 (56). IR (neat): 2955, 2870, 1460, 1360, 1170, 1140, 1060, 990, 940, 870, 750 cm^{-1}.

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Preparation of an Aromatic Synthon for Maytansinoid Synthesis†

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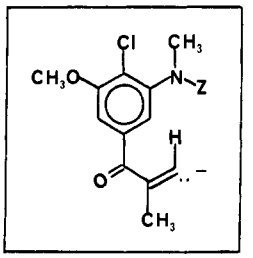
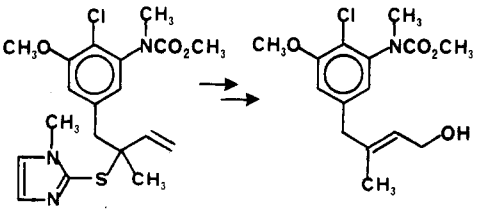
Maytansine is a complex, antileukemic natural product[1] whose total synthesis has been achieved in three laboratories[2] thus far. Several maytansine congeners have been discovered which are oxygenated on carbon number 15 (maytansine numbering system[1]).[3] A synthon for the vinyl anion 1 should be a useful reagent for the construction of 15-oxygenated maytansinoids, and this paper details the preparation and alkylation of such a reagent.



1

A number of reports deal specifically with the preparation of aromatic maytansinoid moieties,[2b,4] and one of these involves a [2,3]-sigmatropic rearrangement. Ho has described[4d] the preparation of allylic sulfide 2 from 2-amino-5-methylphenol, as well as its oxidation and rearrangement to the sulfenate ester, followed by desulfurization to provide alcohol 3.



2 3

The present paper details a similar allylic sulfoxide–sulfenate ester rearrangement and is an extension of earlier model studies.[5] Herein is described the preparation of

† Dedicated to Professor Ernest Wenkert on the occasion of his 60th birthday.

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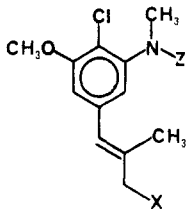
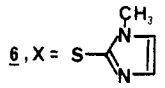
a simple (*E*)-1-aryl-2,3-dimethyl-2-propen-1-one in which the aryl group possesses the maytansine substituent pattern. An important feature of this synthesis route is the regioselective alkylation of an allylic sulfide anion in which a secondary amino group is protected as its lithium salt.

In analogy to the earlier report[5] an appropriately substituted α-methylcinnamaldehyde served as the starting point for the synthesis. (*E*)-3-[4-Chloro-3-methoxy-5-(methylamino)phenyl]-2-methyl-2-propenal was prepared from methyl vanillate by using the procedures of Bernauer, Schneider, and their co-workers[4e] (see also ref 2b). Carbonyl reduction and N-derivatization provided alcohols **4**.[6] These were converted[7] to the corresponding allylic chlorides **5**, which were reacted with 2-mercapto-1-methylimidazole[8] in sodium methoxide/methanol to provide allylic sulfides **6**.

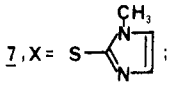


4, X = OH; **5**, X = Cl;



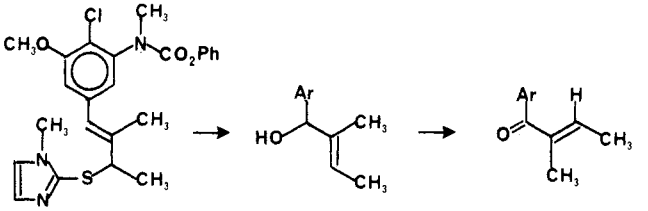
6, X = S

(**a**. Z = CO_2CH_3; **b**. Z = $COCF_3$)



7, X = S ; Z = H

Because of difficulties encountered in several attempts to cleanly metalate and alkylate carbamate **6a**, amide **6b** was prepared and transformed into the free amine **7**.[9] Treatment with 2 equiv of *n*-butyllithium followed by sequential addition of 1 equiv of phenyl chloroformate provided the desired allylic sulfide **8**. As expected, initial alkylation occurred on carbon, allowing subsequent carbamoylation on nitrogen. This product was easily oxidized (*m*-chloroperoxybenzoic acid) to the allylic sulfoxide, whose equilibrium with the corresponding sulfenate ester was disrupted through the agency of diethylamine to provide the alcohol **9**.[5,8] Oxidation with manganese dioxide afforded the target compound, enone **10** (the aryl group in structures **9** and **10** is identical with that of structure **8**).



8 **9** **10**

Thus, the allylic sulfide **7** has been demonstrated to serve as a synthon for the hypothetical anion **1**. It should play a useful role in subsequent synthesis endeavors that are directed toward the 15-oxygenated maytansinoids.[3]

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Pye-Unicam SP-1000 spectrophotometer. ^1H NMR spectra were run on $CDCl_3$ solutions with Me_4Si as an internal standard (δ 0) on a Varian EM-360A spectrometer. Preparative TLC utilized Merck 60 GF_{254} or Sigma Type GF (10–40 μm) silica gel as the adsorbent. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Mass spectral data were provided by the Midwest Center for Mass Spectrometry at the University of Nebraska—Lincoln. Solutions of potassium carbonate, sodium bicarbonate, and sodium chloride were aqueous and saturated. Solutions of unpurified reaction products were dried over anhydrous sodium sulfate. Tetrahydrofuran was distilled from lithium aluminum hydride immediately before use. 2-Mercapto-1-methylimidazole and *n*-butyllithium were purchased from the Aldrich Chemical Co.

(*E*)-3-[4-Chloro-3-methoxy-5-(methylamino)phenyl]-2-methyl-2-propen-1-ol. Sodium borohydride (2.126 g, 0.0562 mol) was added in portions to a stirred solution of (*E*)-3-[4-chloro-3-methoxy-5-(methylamino)phenyl]-2-methyl-2-propenal[4e] (1.843 g, 7.700 mmol) in 70 mL of methanol which was chilled in an ice/salt bath. Stirring at 0–5 °C was continued for 3 h, at which time methanol was removed (rotary evaporator). The residue was transferred to a separatory funnel with 125 mL of ether, washed with water and brine, and then dried. Removal of solvent left 1.823 g (98%) of the desired allylic alcohol which was routinely used directly in the next reaction. Purification by preparative TLC (R_f 0.58; ethyl acetate) provided the alcohol (83%) as a pale yellow liquid: IR 3625 (w), 3450 (w), 1582 (s) cm^{-1}; ^1H NMR δ 1.87 (s, 3 H, olefinic Me), 2.79 (s, 3 H, NMe), 3.35 (br s, 1 H, NH), 3.74 (s, 3 H, OMe), 4.08 (s, 2 H, CH_2), 4.29 (br s, 1 H, OH), 6.15 (s, 2 H, aromatic H), 6.24 (s, 1 H, olefinic H); mass spectrum, *m/e* 243 (M^+), 241 (M^+, base), 224, 212, 198; exact mass, *m/e* 241.0877 (calcd for $C_{12}H_{16}{}^{35}ClNO_2$, 241.0869).

(*E*)-*N*-[2-Chloro-5-(3-hydroxy-2-methyl-1-propenyl)-3-methoxyphenyl]-2,2,2-trifluoro-*N*-methylacetamide (4b). This procedure was adapted from one by Newman.[10] Trifluoroacetic anhydride (16.750 g, 0.0798 mol) was added dropwise over 5 min to a stirred mixture of 1.675 g (6.948 mmol) of amino alcohol (prepared as described above) and 8.392 g (7.918 mmol) of anhydrous sodium carbonate in 60 mL of ether which was chilled in an ice/salt bath. After 15 min the ice bath was removed. After an additional 15 min, the mixture was poured over ice and extracted thrice with chloroform. The combined chloroform extracts were washed with water and brine and then dried. Evaporation of the solvent left 2.954 g (98%) of the bis(tri-

(1) Komoda, Y.; Kishi, T. In "Anticancer Agents Based on Natural Product Models"; Cassady, J. M., Douros, J. D., Eds.; Academic Press: New York, 1980; p 353.

(2) (a) Corey, E. J.; Weigel, L. O.; Chamberlin, A. R.; Cho, H.; Hua, D. H. *J. Am. Chem. Soc.* **1980**, *102*, 6613. (b) Meyers, A. I.; Babiak, K. A.; Campbell, A. L.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. D. *Ibid.* **1983**, *105*, 5015. (c) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *Ibid.* **1984**, *106*, 3252.

(3) Inter alia note the following: (a) Wani, M. C.; Taylor, H. L.; Wall, M. E. *J. Chem. Soc., Chem. Commun.* **1973**, 390. (b) Powell, R. G.; Weisleder, D.; Smith, C. R.; Kozlowski, J.; Rohwedder, W. K. *J. Am. Chem. Soc.* **1982**, *104*, 4929.

(4) (a) Foy, J. E.; Ganem, B. *Tetrahedron Lett.* **1977**, 775. (b) Corey, E. J.; Wetter, H. F.; Kozikowski, A. P.; Rao, A. V. R. *Ibid.* **1977**, 777. (c) Corey, E. J.; Bock, M. G.; Kozikowski, A. P.; Rao, A. V. R. *Ibid.* **1978**, 1051. (d) Ho, P.-T. *Can. J. Chem.* **1980**, *58*, 861. (e) Götschi, E.; Schneider, F.; Wagner, H.; Bernauer, K. *Org. Prep. Proced. Int.* **1981**, *13*, 23. (f) Kitamura, M.; Isobe, M.; Ichikawa, Y.; Goto, T. *J. Org. Chem.* **1984**, *49*, 3517.

(5) Goodwin, T. E.; Ratcliff, D. G.; Crowder, C. M.; Seitzinger, N. K. *J. Org. Chem.* **1982**, *47*, 815.

(6) Carbamate **4a** was prepared by adapting a procedure used by Corey et al.[4c] to produce a similar compound. Unlike the literature example, reaction at oxygen was not a problem in this case. Conversely, amide **4b** was routinely obtained following a separate step to selectively remove residual *O*-acyl groups (see the Experimental Section). Direct N-derivatization of the cinnamaldehyde precursor was inefficient.

(7) (a) Hwang, C. K.; Li, W. S.; Nicolaou, K. C. *Tetrahedron Lett.* **1984**, 2295. (b) Collington, E. W.; Meyers, A. I. *J. Org. Chem.* **1971**, *36*, 3044.

(8) Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147.

(9) The purified amine **7** can be prepared in an overall yield of 55% from the corresponding α-methylcinnamaldehyde with no purification of intermediate products.

(10) Newman, H. *J. Org. Chem.* **1965**, *30*, 1287.

fluoroacetate) as a yellow liquid: ^{1}H NMR δ 1.95 (s, 3 H, olefinic Me), 3.29 (s, 3 H, NMe), 3.90 (s, 3 H, OMe), 4.88 (s, 2 H, CH_2), 6.55 (s, 1 H, olefinic H), 6.90 (s, 2 H, aromatic H).

This unpurified product was stirred at the ambient temperature in 60 mL of methanol and 20 mL of pH 10 buffer (Sargent-Welch) for 1 h and then diluted with 225 mL of water and extracted with two 225-mL portions of ether. The combined ether extracts were washed with water and brine and then dried. Evaporation of the solvent left 2.253 g (96%) of alcohol **4b** as a golden oil that was routinely used directly in the next reaction. Purification by preparative TLC (R_f 0.41–0.74; ethyl acetate) provided **4b** (77% overall from amino alcohol) as a pale yellow liquid. On a few occasions the product solidified, and recrystallization from methanol/water gave off-white crystals: mp 72.5–73.5 °C; IR 3550 (w), 1704 (s), 1592 (w), 1580 (w) cm^{-1}; ^{1}H NMR δ 1.76 (s, 3 H, olefinic Me), 2.40 (s, 1 H, OH), 3.28 (s, 3 H, NMe), 3.88 (s, 3 H, OMe), 4.15 (s, 2 H, CH_2), 6.45 (s, 1 H, olefinic H), 6.82 (s, 2 H, aromatic H). Anal. Calcd for $C_{14}H_{15}ClF_3NO_3$: C, 49.79; H, 4.48. Found: C, 49.95; H, 4.50.

(*E*)-*N*-[2-Chloro-5-(3-chloro-2-methyl-1-propenyl)-3-methoxyphenyl]-2,2,2-trifluoro-*N*-methylacetamide (5b). This procedure is adapted from work by Nicolaou et al.[7a] 4-(Dimethylamino)pyridine (0.324 g, 2.652 mmol), *p*-toluenesulfonyl chloride (0.996 g, 5.222 mmol), and triethylamine (0.72 mL, 5.17 mmol) were added to a stirred solution of 1.200 g (3.556 mmol) of unpurified alcohol **4b** in 14 mL of dichloromethane. Stirring under nitrogen at ambient temperature was continued for 2 h. The mixture was diluted with 700 mL of ether, washed with 200-mL portions of saturated copper(II) sulfate solution until the characteristic dark blue color of the pyridine complex was absent, washed with sodium bicarbonate solution and brine, and then dried. Evaporation of solvent left the allylic chloride **5b** (901 mg, 71%) as a yellow liquid that was routinely used directly in the next reaction. Purification by preparative TLC (R_f 0.46–0.68; chloroform) gave **5b** (65%) as a pale yellow liquid that slowly solidified. Recrystallization from pentane/ether gave colorless needles: mp 73.5–74.5 °C; IR 1712 (s), 1578 (m), 1173 (s), 1098 (m) cm^{-1}; ^{1}H NMR δ 1.96 (s, 3 H, olefinic Me), 3.27 (s, 3 H, NMe), 3.86 (s, 3 H, OMe), 4.10 (s, 2 H, CH_2), 6.46 (s, 1 H, olefinic H), 6.81 (s, 2 H, aromatic H). Anal. Calcd for $C_{14}H_{14}Cl_2F_3NO_2$: C, 47.21; H, 3.96. Found: C, 47.30; H, 4.04.

(*E*)-*N*-[2-Chloro-3-methoxy-5-[2-methyl-3-[(1-methyl-1*H*-imidazol-2-yl)thio]-1-propenyl]phenyl]-2,2,2-trifluoro-*N*-methylacetamide (6b). 2-Mercapto-1-methylimidazole (0.180 g, 1.577 mmol) was added to a stirring solution of sodium methoxide (0.085 g, 1.574 mmol) in 2 mL of methanol that was chilled in an ice/salt bath and protected from moisture by a $CaCl_2$ drying tube. After 5 min a solution of 0.534 g (1.500 mmol) of allylic chloride **5b** in 4 mL of methanol was added in one portion, and the mixture was stirred and allowed to come to room temperature over 22 h. The milky yellow solution was diluted with 120 mL of water and extracted thrice with 60-mL portions of ether. The combined ether extracts were washed sequentially with 10% aqueous NaOH, water, and brine and dried. Evaporation of the solvent left 0.579 g (89%) of the allylic sulfide **6b** as a yellow solid. Two recrystallizations from ether provided the analytical sample as colorless crystals: mp 123–124 °C; IR ($CHCl_3$) 1710 (s), 1172 (s), 1098 (m) cm^{-1}; ^{1}H NMR δ 1.97 (s, 3 H, olefinic Me), 3.23 (s, 3 H, NMe), 3.54 (s, 3 H, imidazole NMe), 3.65 (s, 2 H, CH_2), 3.85 (s, 3 H, OMe), 6.00 (s, 1 H, olefinic H), 6.62 (s, 2 H, phenyl H), 6.85 (s, 1 H, imidazole H), 7.02 (s, 1 H, imidazole H). Anal. Calcd for $C_{18}H_{19}ClF_3N_3O_2S$: C, 49.83; H, 4.41. Found: C, 49.82; H, 4.53.

Methyl (*E*)-[2-Chloro-3-methoxy-5-[2-methyl-3-[(1-methyl-1*H*-imidazol-2-yl)thio]propenyl]phenyl]methylcarbamate (6a). Allylic sulfide **6a** was prepared from (*E*)-3-[4-chloro-3-methoxy-5-(methylamino)phenyl]-2-methyl-2-propenal by using a reaction sequence similar to that used in the preparation of compound **6b** (see ref 6) in an overall yield of 85%. The analytical sample was prepared by preparative TLC (R_f 0.18–0.50; 95:5, ether/methanol) to give a yellow liquid: IR ($CHCl_3$) 1705 (s), 1572 (m), 1458 (m), 1166 (m), 1090 (m) cm^{-1}; ^{1}H NMR δ 1.94 (s, 3 H, olefinic Me), 3.10 (s, 3 H, NMe), 3.50 (s, 6 H, imidazole NMe and carbamate OMe), 3.60 (s, 2 H, CH_2), 3.75 (s, 3 H, OMe), 5.99 (s, 1 H, olefinic H), 6.62 (br s, 2 H, phenyl H), 6.92 (s, 1 H, imidazole H), 7.01 (s, 1 H, imidazole H); mass spectrum, *m/e* 397 (M^+), 395 (M^+), 362, 250 (base), 222, 187, 153, 114; exact mass, *m/e* 395.1072 (calcd for $C_{18}H_{22}{}^{35}ClN_3O_3S$, 395.1070).

(*E*)-2-Chloro-3-methoxy-*N*-methyl-5-[2-methyl-3-[(1-methyl-1*H*-imidazol-2-yl)thio]-1-propenyl]benzenamine (7). This procedure is based on an analogous one by Newman.[10] A mixture of the crystalline trifluoroacetamide **6b** (0.586 g, 1.352 mmol), potassium carbonate sesquihydrate (1.10 g, 6.66 mmol), 6 mL of methanol, and 2.5 mL of water was stirred at the ambient temperature for 16 h, diluted with 150 mL of water, and extracted with three 50-mL portions of ether. The combined ether extracts were washed with brine and dried. Evaporation of the solvent left a pale yellow, viscous oil from which the secondary amine **7** was isolated in 93% yield by preparative TLC (R_f 0.31–0.66; ethyl acetate) as a pale yellow liquid; IR (neat) 3450 (m), 2960 (m), 1595 (s), 1465 (s), 1415 (s), 1260 (s), 1180 (s), 1075 (s) cm^{-1}; ^{1}H NMR δ 2.01 (s, 3 H, olefinic Me), 2.85 (s, 3 H, NMe; this peak often appears as a doublet), 3.56 (s, 3 H, imidazole NMe), 3.68 (s, 2 H, CH_2), 3.82 (s, 3 H, OMe), 6.09 (s, 3 H, two phenyl H and olefinic H), 6.93 (s, 1 H, imidazole H), 7.11 (s, 1 H, imidazole H); mass spectrum, *m/e* 339 (M^+), 337 (M^+), 304, 224, 189 (base), 174; exact mass, *m/e* 337.1022 (calcd for $C_{16}H_{20}{}^{35}ClN_3OS$, 337.1015).

Phenyl (±)-(*E*)-[2-Chloro-3-methoxy-5-[2-methyl-3-[(1-methyl-1*H*-imidazol-2-yl)thio]-1-butenyl]phenyl]methylcarbamate (8). A 1.6 M solution of *n*-butyllithium in hexane (0.75 mL; 1.2 mmol of *n*-butyllithium) was added to 10 mL of dry tetrahydrofuran (THF) that was stirred under argon at −78 °C. This was followed by the dropwise addition of sulfide **7** (0.192 g, 0.569 mmol) as a solution in 3 mL of THF. Stirring at −78 °C was continued for 0.5 h, at which time the mixture was orange. A solution of iodomethane (0.081 g, 0.571 mmol) in 1 mL of THF was added dropwise, and the mixture became a translucent, golden color. After an additional 1.5 h at −78 °C, a solution of phenyl chloroformate (0.134 g, 0.856 mmol) in 3 mL of THF was added dropwise, and the clear yellow solution was stirred for an additional 0.5 h. The cooling bath was removed and the mixture was allowed to warm to 20 °C over 0.5 h, at which time 0.5 mL of saturated ammonium chloride solution was added. After 5 min, the mixture was diluted with ether (150 mL), washed with brine, and dried. Removal of solvent left a golden oil from which carbamate **8** was isolated as a white solid in 54% yield[11] by two successive preparative TLCs (R_f 0.22–0.83, ethyl acetate; 0.06–0.19, ether). Recrystallization from ether provided the analytical sample: mp 130–131.5 °C; IR ($CHCl_3$) 1725 (s), 1575 (m) cm^{-1}; ^{1}H NMR δ 1.53 (d, 3 H, J = 7 Hz, Me), 1.99 (s, 3 H, olefinic Me), 3.29 (s, 3 H, carbamate NMe), 3.57 (s, 3 H, imidazole NMe), 3.88 (s, 3 H, OMe), 4.12 (q, 1 H, J = 7 Hz, methine), 6.01 (s, 1 H, olefinic H), 6.60–7.50 (m, 9 H, aromatic H). Anal. Calcd for $C_{24}H_{26}ClN_3O_3S$: C, 61.07; H, 5.55. Found: C, 61.24; H, 5.63.

Phenyl (±)-(*E*)-[2-Chloro-5-(1-hydroxy-2-methyl-2-butenyl)-3-methoxyphenyl]methylcarbamate (9). A solution of 0.052 g of 80–85% *m*-chloroperoxybenzoic acid (0.241–0.256 mmol) in 2 mL of dichloromethane was added dropwise over 2–3 min to a stirred solution of allylic sulfide **8** (0.108 g, 0.229 mmol) in 2 mL of dichloromethane that was chilled in an ice bath. Stirring under a drying tube at 0–5 °C was continued for 0.5 h, when a mixture of 0.3 mL of diethylamine and 0.8 mL of methanol was added. The ice bath was removed and stirring was continued for 23 h. The mixture was diluted with 100 mL of ether, washed sequentially with water, 10% HCl, potassium carbonate solution and brine, and dried. Evaporation of solvent afforded 82 mg (95%) of the alcohol **9** as a pale golden liquid: IR ($CHCl_3$) 3470 (w), 1724 (s), 1590 (m) cm^{-1}; ^{1}H NMR δ 1.49 (s, 3 H, Me α to OH carbon), 1.54 (d, 3 H, J = 7 Hz, Me β to OH carbon), 2.90 (br s, 1 H, OH), 3.27 (s, 3 H, NMe), 3.86 (s, 3 H, OMe, 5.03 (s, 1 H, methine), 5.65 (br q, 1 H, J = 7 Hz, olefinic H), 6.82–7.43 (m, 7

(11) The low yield of carbamate **8** is due only to as yet unresolved difficulties in the carbamoylation step. Quenching the reaction with ammonium chloride solution immediately after the methyl iodide step leads to the isolation of the corresponding free amine *quantitatively* by preparative TLC (R_f 0.51–0.80, ethyl acetate) as a pale yellow liquid: IR ($CHCl_3$) 3460 (w), 1585 (s), 1455 (s), 1415 (m), 1255 (m), 1165 (m), 1090 (m) cm^{-1}; ^{1}H NMR δ 1.51 (d, 3 H, J = 7 Hz, Me), 2.00 (s, 3 H, olefinic Me), 2.84 (d, 3 H, J = 4 Hz, NMe), 3.58 (s, 3 H, imidazole NMe), 3.85 (s, 3 H, OMe), 4.08 (q, 1 H, J = 7 Hz, methine), 6.03 (br s, 3 H, two phenyl H and olefinic H), 6.97 (s, 1 H, imidazole H), 7.16 (s, 1 H, imidazole H); mass spectrum, *m/e* 353 (M^+), 351 (M^+) 251, 237, 202, 167, 114 (base); exact mass, *m/e* 351.1168 (calcd for $C_{17}H_{22}{}^{35}ClN_3OS$, 351.1172).

H, aromatic H). The unpurified product was used directly in the next reaction.

Phenyl (*E*)-[2-Chloro-3-methoxy-5-(2-methyl-1-oxo-2-butenyl)phenyl]methylcarbamate (10). Unpurified allylic alcohol **9** (0.072 g, 0.192 mmol) and 0.335 g of activated manganese(IV) oxide (Aldrich) were stirred at room temperature in 4.5 mL of benzene for 20 h. The mixture was filtered over Celite, concentrated, and purified by preparative TLC (R_f 0.30–0.43; 1:1, ether/petroleum ether) to yield pure ketone **10** (89% overall from **8**) as a pale yellow liquid: IR ($CHCl_3$) 1724 (s), 1643 (m), 1570 (m) cm^{-1}; ^1H NMR δ 1.89 (d, 3 H, J = 6.8 Hz, β-Me), 1.97 (s, 3 H, α-Me), 3.32 (s, 3 H, NMe), 3.96 (s, 3 H, OMe), 6.45 (br q, 1 H, J = 6.8 Hz, olefinic H), 6.92–7.61 (m, 7 H, aromatic H); mass spectrum, m/e 373 (M^+), 338, 280 (base), 252, 217; exact mass, m/e 373.1090 (calcd for $C_{20}H_{20}{}^{35}ClNO_4$, 373.1081).

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Facile Conversion of 4(5)-Nitro-5(4)-methylimidazoles into 4(5)-Nitro-5(4)-cyanoimidazoles

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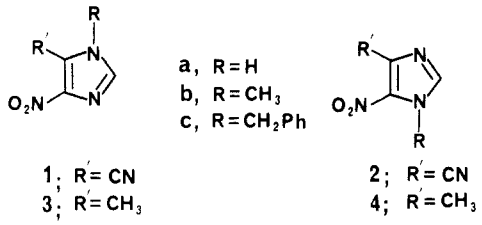
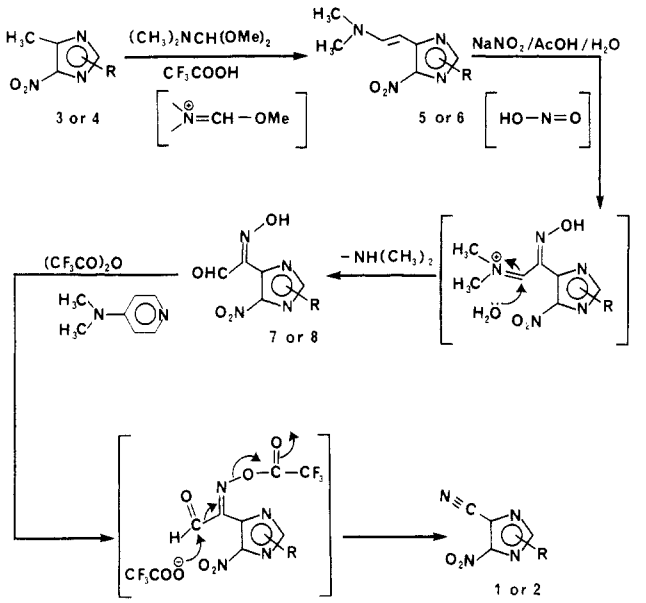
5(4)-Cyano-4(5)-nitroimidazoles (**1**, **2**) are important synthons in the preparation of imidazole fused heterocycles.[1] These compounds offer the option of chain extension either as electrophiles involving their cyano function or as nucleophiles after reduction of their nitro group. While **1** can be prepared from straight-chain precursors, albeit in multisteps and poor yields,[1b] no method to date is available for the synthesis of the (biologically more significant) isomer **2**, which is a potential precursor for the ubiquitous 9-substituted purines. We report here a facile general method for the synthesis of both **1** and **2**, in a three-step procedure, from the readily accessible 5(4)-methyl-4(5)-nitroimidazoles **3** and **4**, respectively.

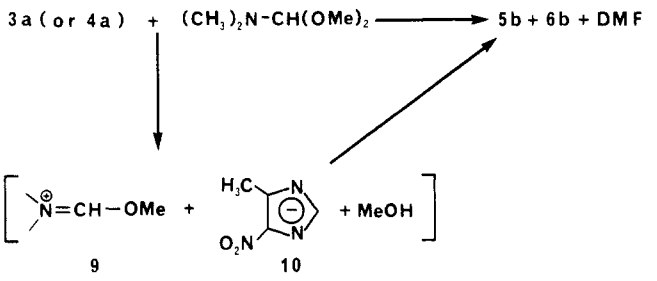


(1) (a) Prasad, R. N.; Robins, R. K. *J. Am. Chem. Soc.* **1957**, *79*, 6401. (b) Sarasin, J.; Wegmann, E. *Helv. Chim. Acta* **1924**, *7*, 713. (c) Mann, F. G.; Porter, J. W. G. *J. Chem. Soc.* **1945**, 751 and the references cited therein.

Scheme I



Scheme II



Our method (Scheme I) consists of reacting **3** or **4** (R = alkyl) with dimethylformamide dimethyl acetal, catalyzed by trifluoroacetic acid, to obtain the corresponding 5(4)-β-(*N*,*N*-dimethylamino)ethylene-4(5)-nitroimidazoles **5** or **6**, respectively, in 75–80% yields. The enamine **5** or **6** was further treated with sodium nitrite in aqueous acetic acid to yield the corresponding glyoxal α-oximes **7** or **8**, respectively, in 74–94% yields. The latter compounds, upon treatment with trifluoroacetic anhydride, catalyzed by 4-(*N*,*N*-dimethylamino)pyridine, afforded the title cyanoimidazoles **1** or **2**, respectively, in 60–80% yields. The structures of the products in each step were confirmed by ^1H NMR, IR, mass spectral data and elemental microanalyses. The presumed key intermediates of these reactions are shown in brackets. In general, the proton NMR signals of both the ring alkyl (aralkyl) and the imidazole CH groups were shifted downfield by approximately 0.2–0.3 ppm in **6** as compared with **5**. A similar trend was discernible between **8** and **7**. However, the difference was less dramatic between the signals of **2** and **1**. While in the former two cases only the NO_2 group exerted the proximal deshielding effect, this phenomenon was shared by both C≡N and NO_2 in the last instance, thus causing less difference between the chemical shifts of **2** and **1**. The IR spectra of the final products revealed strong nitrile absorptions in the 2200-cm^{-1} region.

The reaction of the unsubstituted **3** or **4** (R = H) with dimethylformamide dimethyl acetal directly provided a mixture of **5** and **6** (R = Me) in approximately 1:1 ratio (Scheme II). This reaction required no acid catalyst unlike that of the substituted **3** or **4** (R = alkyl) with DMF acetal, as described above. The mixture was separated by either fractional recrystallization or flash chromatography. The positions of alkylation in **5b** and **6b** were established (a)

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