76-05-1; allyl bromide, 106-95-6; methallyl chloride, 1458-98-6; (*E*)-2-butenyl bromide, 29576-14-5; (*Z*)-2-butenyl bromide, 39616-19-8; 3-bromo-1-butene, 22037-73-6; γ,γ-dimethylallyl bromide, 870-63-3.

Efficient, Trimethylsilyl Triflate Mediated Conversion of Diels-Alder Adducts of 1-Methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (Danishefsky's Diene) to Cyclohexenones[1a]

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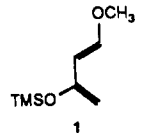
Since its introduction in 1974,[2] 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene (Danishefsky's diene, 1) has been successfully employed in a wide variety of synthetic efforts.[3-6] The foremost synthetic application of 1 continues to be the Diels-Alder synthesis of cyclohexenones.



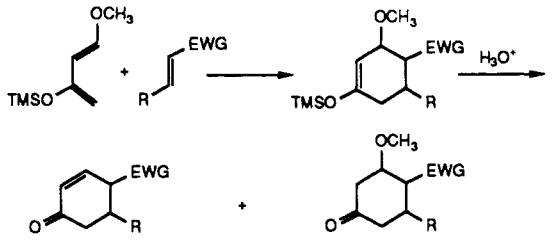
1

Heretofore, the conversion of Diels-Alder adducts of Danishefsky's diene to cyclohexenones has been accomplished simply by treatment with aqueous acid. However, this method sometimes suffers from the formation of a methoxy ketone as the sole product or admixed with the desired enone (Scheme I).[7]

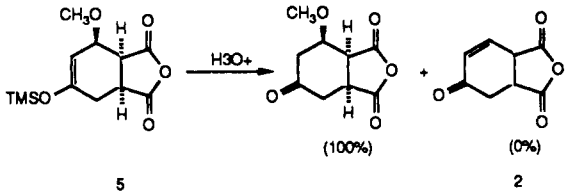
The enone and methoxy ketone products appear to arise via competing hydrolysis pathways. Hydrolysis to enone can occur via stepwise or concerted formal elimination of methanol. Enone formation thus competes with simple hydrolysis of the silyl enol ether, which affords β-methoxy ketone. Danishefsky has shown that the methoxy ketones generally are not converted to enones under acid hydrolysis conditions.[4c,8] Accordingly, the enone and methoxy ketone probably arise through competitive C- and O-protonation of adduct.

Danishefsky has further shown that the amount of methoxy ketone formed in the hydrolysis is dependent upon the concentration of the acid and on specific structural features of the adducts.[4c] Dilute acid (4:1 THF/0.5 N HCl) was found to minimize methoxy ketone formation in many cases, whereas more concentrated acid led to a

Scheme I



Scheme II



5 2

Scheme III

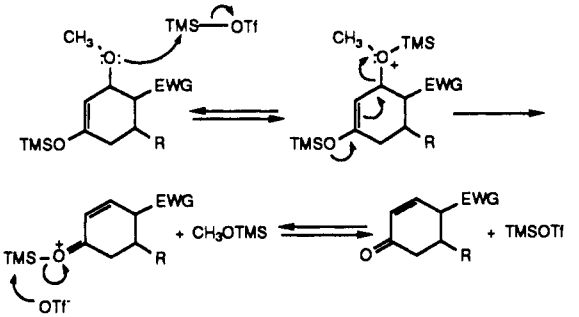
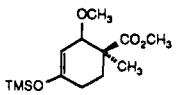
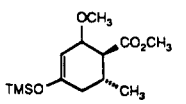
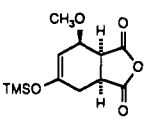


Table I. Comparison of Product Yields for Acid Hydrolysis and Catalytic TMSOTf

	0.005 N HCl[a]		TMSOTf	
	% methoxy ketone	% enone	% methoxy ketone	% enone
 3[b]		65	0	95
 4[b]	20	10[c]	0	93[d]
 5[e]	100	0	0	98

[a] Reference 4c. [b] Exo endo mixture. [c] 1:1 mixture of 8 and 9. [d] 27.5:1 mixture of 8 and 9. [e] Reference 9.

(1) (a) This material taken from the Ph.D. Thesis of the author. (b) Present address: Department of Chemistry, United States Air Force Academy, Colorado Springs, CO 80840.

(2) Kitahara, T.; Danishefsky, S. *J. Am. Chem. Soc.* **1974**, *96*, 7807-7808.

(3) For a review of Danishefsky's earlier work with 1 and other silyloxy dienes, see: Danishefsky, S. *Acc. Chem. Res.* **1981**, *14*, 400-406.

(4) (a) Kitahara, T.; Danishefsky, S. *J. Org. Chem.* **1975**, *40*, 538-539. (b) Kitahara, T.; Schuda, P. F.; Etheredge, S. J.; Danishefsky, S. *J. Am. Chem. Soc.* **1976**, *98*, 3028-3030. (c) Kitahara, T.; Yan, C. F.; Morris, J.; Danishefsky, S. *J. Am. Chem. Soc.* **1979**, *101*, 6996-7000. (d) Hirama, M.; Gomblatz, K.; Harayama, T.; Berman, E.; Danishefsky, S. *J. Am. Chem. Soc.* **1979**, *101*, 7020-7031. (e) Morris, J.; Mullen, G.; Gammill, R.; Danishefsky, S. *J. Am. Chem. Soc.* **1980**, *102*, 2838-2840.

(5) (a) Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. *J. Am. Chem. Soc.* **1978**, *100*, 2929-2930. (b) Holmes, A. M.; Johnson, I.; ApSimon, J. W. *Can. J. Chem.* **1982**, *60*, 308-316. (c) Belanger, J.; Landry, J. R.; Pare, J.; Jankowski, K. *J. Org. Chem.* **1982**, *47*, 3649-3652. (d) Kinney, W. A.; Crouse, G. D.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 4986-5000. (e) Simpkins, N. S.; Whittle, A. J.; Ley, S. V. *J. Chem. Soc., Chem. Commun.* **1983**, 503-505. (f) Rosen, T.; Taschner, M. J.; Thomas, J. A.; Heathcock, C. H. *J. Org. Chem.* **1985**, *50*, 1190-1201.

(6) See, for example: (a) Kobayashi, S.; Kerwin, J. F., Jr.; Danishefsky, S. *J. Am. Chem. Soc.* **1982**, *104*, 358-359. (b) Uang, B. J.; Quallich, G.; Harvey, D. F.; Danishefsky, S. *J. Org. Chem.* **1984**, *49*, 393-395. (c) Uang, B. J.; Quallich, G.; Danishefsky, S. *J. Am. Chem. Soc.* **1984**, *106*, 2453-2455. (d) Harvey, D. F.; Pearson, W. H.; Danishefsky, S. *J. Am. Chem. Soc.* **1984**, *106*, 2455-2458.

(7) For examples, see refs 4 and 5.

(8) Methanol can be eliminated by repeated exposure to neutral alumina; see ref 4c.

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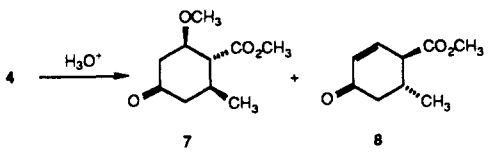
Scheme IV



7 8

greater percentage of side product. However, methoxy ketone formation remained problematic for several cases even when the optimal dilute acid conditions were employed.[4c] For example, the maleic anhydride adduct afforded methoxy ketone as the sole product (Scheme II).[4c,9] Danishefsky also noted that the hydrolytic fate of adducts was influenced by the nature of substituent R and its stereochemical relationship to the methoxy group (Scheme I).[4c]

We became interested in this problem in connection with recent work wherein an annoying methoxy ketone side product was encountered.[10] That difficulty was circumvented by employing a catalytic amount of trimethylsilyl triflate (TMSOTf) in lieu of dilute acid hydrolysis (Scheme III).[11]

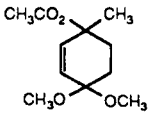
Methoxy ketone formation is unlikely under these conditions, in part because C-silylation of an adduct is disfavored in consequence of the oxophilicity of silicon. Additionally, any silyl ketone formed simply reconverts to starting material. In contrast, under acidic conditions, silyl enol ether hydrolysis is irreversible.

Results and Discussion

Adducts **3**, **4**, and **5** were prepared from **1** and methyl methacrylate, methyl *trans*-crotonate, and maleic anhydride, respectively, and converted to enones (Table I). Acid hydrolyses of these adducts were reportedly problematical with respect to methoxy ketone formation and/or enone yield.[4c]

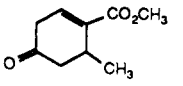
Our general procedure involves exposing the adduct to a dilute methylene chloride solution of TMSOTf, acetone (vide infra), and a proton scavenger such as collidine at −78 °C for up to 15 min, followed by workup. Toluene was found to be slightly less effective as a solvent; use of THF or hexanes resulted in lower yields.

A contaminant in the initial TMSOTf-catalyzed reactions of **3** was ketal **6**. The appearance of **6** was not unexpected because TMSOTf and the byproduct MeOTMS have been previously employed in an efficient ketalization method.[12] Routine addition of acetone prior to TMSOTf introduction, presumably resulting in ketalization of acetone rather than product enone, circumvented the formation of ketal side products in all cases. The volatile acetone ketal was subsequently removed during workup.



6

Dilute acid hydrolysis of **4** reportedly afforded a 2:1 mixture of methoxy ketone **7** and enone **8** in low yield (Scheme IV).[4c] Subsequently the enone isomerized to a 1:1 mixture of **8** and **9** (apparently during normal silica gel chromatography). Our initial experiments were also frustrated by the formation of these isomeric enones. The use of acidic silica gel for chromatography, as described in the Experimental Section, was found to preserve our initial 27:1 ratio of **8**:**9**.



9

The use of TMSOTf with **5** gave vastly different results than did acidic hydrolysis. No methoxy ketone was detected and the yield of the hitherto unknown enone **2** was virtually quantitative.

Experimental Section

All reactions and recrystallizations involving air- or moisture-sensitive materials were carried out under an atmosphere of argon. Glass connectors, Teflon plugs (Ace threaded), and FETFE o-rings were obtained from Ace Glass Inc. The connectors were joined to heavy-walled glass tubing to form resealable tubes that could conveniently be opened for monitoring the progress of reactions. The tubes were washed with base and oven- or flame-dried prior to use.

Thin layer chromatography plates (silica, 0.25 mm layer) were purchased from E. Merck. Silica (230–400 mesh) from E. Merck was employed in flash chromatography. Capillary gas chromatography analyses were performed with a Hewlett Packard 5890 instrument equipped with a 25 m × 0.31 mm fused silica column containing cross-linked 5% phenyl methyl silicone (SE-54), 0.52 μm layer thickness.

Infrared spectra were obtained with a Perkin-Elmer Model 727 B spectrophotometer; frequencies of selected bands are reported in cm^{-1}. ^1H NMR spectra were measured on a Magnachem A-200 or Bruker WM-250 spectrometer operating at 199.5 or 250.2 MHz, respectively. Chemical shifts are reported in ppm (δ), referenced to tetramethylsilane or deuteriochloroform (0.00 and 7.24, respectively). All coupling constants are given in hertz. ^{13}C NMR spectra were obtained with the same instruments operating at 50.1 or 62.9 MHz, respectively, and were referenced to internal deuteriochloroform (77.0 ppm). Mass spectra were obtained on Hewlett Packard 5980A or Varian MAT CH5 instruments. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected.

Methylene chloride was distilled from CaH_2 under argon and stored over activated neutral alumina. Acetone was dried three times with 3-Å molecular sieves immediately prior to use.[13] Toluene was distilled from CaH_2 under argon and stored over 3-Å molecular sieves. Benzene was distilled from CaH_2 under argon immediately prior to use.

Collidine (Aldrich) was distilled from CaH_2 under argon and stored over 3-Å molecular sieves at −18 °C. Trimethylsilyl triflate (Aldrich) was transferred via cannula under argon from its shipping ampule to a glass tube sealed with a Teflon stopcock and stored at −18 °C. Methyl methacrylate and methyl crotonate (Aldrich) were distilled under argon and stored over 3-Å molecular sieves at −18 °C. Maleic anhydride (Fisher) was sublimed at 100 °C (15 mmHg).

4-Carbomethoxy-3-methoxy-4-methyl-1-[(trimethylsilyl)oxy]cyclohex-1-ene (3). A solution of diene **1** (4.66 mL, 24.0 mmol) and methyl methacrylate (1.28 mL, 12.0 mmol) in 5 mL of benzene was heated in a heavy-walled glass tube at 95 °C for 24 h. Distillation[14] afforded 2.99 g (91.4% yield) of a clear, light

(9) Kitahara, T.; Schuda, P. F.; Danishefsky, S. *Org. Synth.* **1983**, *61*, 147–150.

(10) Shiner, C. S.; Vorndam, P. E.; Kass, S. R. *J. Am. Chem. Soc.* **1986**, *108*, 5699–5701.

(11) For a review, see: Stang, P. J.; White, M. R. *Aldrichimica Acta* **1983**, *16*, 15–22. See also: Emde, H.; Domsch, D.; Feger, H.; Frick, U.; Gotz, A.; Hergott, H. H.; Hofmann, K.; Kober, K.; Krageloh, T.; Oesterle, W.; Steppan, W.; West, W.; Simchen, G. *Synthesis* **1982**, 1–26.

(12) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, 1357–1359.

(13) (a) Smithers, R. H.; Burfield, D. R. *J. Org. Chem.* **1978**, *43*, 3966–3968. (b) Smithers, R. H.; Gan, G.-H.; Burfield, D. R. *J. Appl. Chem. Biotechnol.* **1978**, *28*, 23–30.

yellow liquid: bp 118-122 °C (5.0 mmHg).

The product was deduced to be a 1:1 mixture of isomers by capillary GC and ^{1}H NMR analysis. No characterization data were reported for the individual components of this mixture in Danishefsky's original report.[4c]

4-Carbomethoxy-4-methylcyclohex-2-en-3-one. In a 10-mL round-bottomed flask, a solution of **3** (0.064 g, 0.235 mmol) and acetone (0.086 mL, 1.175 mmol) in 1 mL of methylene chloride was placed under argon and cooled to -78 °C. TMSOTf (0.19 mL of a 0.06 M methylene chloride solution, 0.0117 mmol) and collidine (0.078 mL of a 0.03 M methylene chloride solution, 0.0023 mmol) were combined in a 10-mL pear-shaped flask under argon and added to the adduct solution via a cannula, resulting in a clear straw-colored solution. After 5 min, the reaction was quenched with an additional 5 equiv of collidine in methylene chloride, poured into a separatory funnel containing 20 mL of cold 1 M pH 7.0 phosphate buffer, and extracted with three 10-mL portions of methylene chloride. The combined extracts were dried over sodium sulfate, filtered, and concentrated. Flash chromatography on 25 g of silica gel, using 20% ethyl acetate/hexanes as eluant, afforded 0.038 g (95.1% yield) of the enone as a clear, colorless liquid: R_f = 0.20 using 20% ethyl acetate/hexanes for development; ^{1}H NMR ($CDCl_3$) identical with published spectrum;[4c] ^{13}C NMR ($CDCl_3$) 24.4, 32.3, 34.2, 43.6, 52.1, 128.4, 151.2, 174.2, 197.6; IR (neat) 2960 (s), 1730 (s), 1680 (s), 1440 (s), 1260 (s), 1200 (s), 1120 (s); mass spectrum 168 (M^+), 140, 112, 109, 81; exact mass calcd for $C_9H_{12}O_3$ 168.0786, found 168.0777.

4-Carbomethoxy-3-methoxy-5-methyl-1-[(trimethylsilyl)oxy]cyclohex-1-ene (4). A solution of diene **1** (4.87 mL, 25.0 mmol) and methyl *trans*-crotonate (1.06 mL, 10.0 mmol) was heated in a heavy-walled glass tube at 120 °C for 30 h. Distillation[14] afforded 2.34 g (86.2% yield) of clear colorless liquid: bp 96-98 °C (0.4 mmHg).

The product was deduced to be a 2:1 mixture of isomers by capillary GC and ^{1}H NMR analysis. Danishefsky et al. obtained an identical ratio and determined the stereochemistry of the adducts by analysis of ^{1}H NMR coupling constants of the appropriate methine protons, although the NMR data were not reported.[4c]

4-Carbomethoxy-5-methylcyclohex-2-en-3-one. In a 10-mL round-bottomed flask, a solution of **4** (0.178 g, 0.652 mmol) and acetone (0.24 mL, 3.26 mmol) in 2 mL of methylene chloride was placed under argon and cooled to -78 °C. TMSOTf (0.54 mL of a 0.06 M methylene chloride solution, 0.032 mmol) and collidine (0.21 mL of a 0.03 M methylene chloride solution, 0.0063 mmol) were combined in a 10-mL pear-shaped flask under argon and then added to the adduct solution via a cannula, resulting in a clear, straw-colored solution. After 5 min, the reaction was quenched with an additional 5 equiv of collidine in methylene chloride and then poured into a separatory funnel containing 30 mL of cold 1 M pH 7.0 phosphate buffer and extracted with three 10-mL portions of methylene chloride. The combined extracts were dried over sodium sulfate, filtered, and concentrated. Acidic silica gel was prepared by stirring 240 g of silica gel with 300 mL of 2 M HCl for 30 min at room temperature. After the supernatant acid was decanted, the moist gel was dried in air at 25 °C overnight and then placed in an oven at 115 °C for 12 h. Flash chromatography on 13 g of this silica gel, using 27% ethyl acetate/hexanes as eluant (R_f = 0.25), afforded 0.101 g (92.8% yield) of a clear colorless liquid, shown to be a 27.5:1 mixture of double bond isomers **8** and **9** (uncorrected capillary GC). For **8**: ^{1}H NMR ($CDCl_3$) 1.03 (d, J = 6.1, 3 H), 2.10 (m, 1 H), 2.38-2.57 (m, 2 H), 3.40 (dt, J = 2.6, 9.0, 1 H), 3.69 (s, 3 H), 5.90 (dd, J = 10, 1 H), 6.79 (dd, J = 10, 1 H); ^{13}C NMR ($CDCl_3$) 19.8, 32.5, 44.4, 49.6, 52.1, 130.0, 145.3, 172.1, 197.8; IR (neat) 2960 (s), 1780 (s), 1710 (s), 1250 (s), 920 (s); mass spectrum 168 (M^+), 126, 109, 98, 81; exact mass calcd for $C_9H_{12}O_3$ 168.0786, found 168.0774.

5-Oxocyclohex-3-ene-1,2-dicarboxylic Acid Anhydride (2). A solution of **5** (0.439 g, 1.63 mmol) and acetone (0.60 mL, 8.15 mmol) in 1.5 mL of methylene chloride was placed under argon in a 25-mL round-bottomed flask and cooled to -78 °C. TMSOTf (1.35 mL of a 0.06 M methylene chloride solution, 0.08 mmol) was added via syringe. After 2 min, volatile materials were removed at -78 °C via vacuum (pump) through a needle. The remaining white solid was washed once with 5 mL of ice-cold 1:1 pentane/ethyl acetate and three times with 5-mL portions of ice-cold pentane. After each washing, the mixture was centrifuged and the supernatant removed via cannula. The remaining solvent was removed through a needle to afford 0.265 g (97% yield) of **2** as white crystals: mp 162-163 °C; ^{1}H NMR (acetone-d_6) 2.94 (m, 2 H), 3.34 (m, 2 H), 5.24 (dd, J = 2.0, 8.1, 1 H), 5.94 (ddd, J = 0.5, 2.8, 8.1, 1 H); ^{13}C NMR (acetone-d_6) 33.7, 39.3, 43.1, 132.5, 140.7, 170.2, 173.5, 193.4; IR (KBr) 3190 (m), 1780 (s), 1740 (s), 1240 (s); mass spectrum 166 (M^+), 138, 122, 94. Anal. Calcd for $C_8H_6O_4$: C, 57.84; H, 3.64. Found: C, 57.78; H, 3.66.

Acknowledgment. I wish to thank Dr. Robert Barkley for mass spectrometric analyses.

(14) Chromatographic purification of these and other adducts on silica gel resulted in the hydrolysis of a small fraction (<5%) of the adduct to methoxy ketone. The presence of any methoxy ketone complicated assessment of the subsequent TMSOTf reactions.

Hydrolysis of Dideoxygenated Purine Nucleosides: Effect of Modification of the Base Moiety[1]

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Dideoxynucleosides are receiving a considerable amount of interest currently because of their ability to inhibit the cytopathic effect of the human immunodeficiency virus (HIV-1), the etiologic agent of AIDS.[2-5] Dideoxyadenosine (ddA) and dideoxyinosine (ddI), members of this class of nucleosides, have potent activity against the AIDS virus and are currently undergoing extensive biological and clinical studies.[5-9] However, both ddA and ddI are unstable with respect to hydrolytic cleavage of the glycosidic bond.[10] This inherent factor limits considerably the usefulness of these compounds as biological probes and antiviral agents. The design of congeners that would be more stable hydrolytically than the parent compounds would be of considerable significance in this area. However, the rational design of such new analogues requires some information on the effect of structural modification on hydrolytic stabilities. Although the hydrolytic stabilities of ribonucleosides have received considerable attention,[11-15]

(1) Presented, in part, at the 197th National Meeting of the American Chemical Society, Dallas, TX, 1989.

(2) Fauci, A. S. *Science* **1988**, *239*, 617.
(3) Herdewijn, P.; Pauwels, R.; Baba, M.; Balzarini, J.; DeClercq, E. *J. Med. Chem.* **1987**, *30*, 2131.
(4) Broder, S., Ed. *AIDS*; Dekkar: New York, 1987.
(5) Dahlberg, J. E.; Mitsuya, H.; Blam, S. B.; Broder, S.; Aaronson, S. A. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 2469.
(6) Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911.
(7) Cooney, D. A.; Ahluwalia, G.; Mitsuya, H.; Fridland, A.; Johnson, M.; Hao, Z.; Dalal, M.; Balzarini, J.; Broder, S.; Johns, D. G. *Biochem. Pharmacol.* **1987**, *36*, 1765.
(8) Mitsuya, H.; Jarrett, R. F.; Matsukura, M.; Veronese, F.; DeVico, A. L.; Sarngadharan, M. G.; Johns, D. G.; Reitz, M. S.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 2033.
(9) Yarchoan, R.; Mitsuya, H.; Thomas, R. V.; Pluda, J. M.; Hartman, N. R.; Perno, C.-F.; Marczyk, K. S.; Allain, J.-P.; Johns, D. G.; Broder, S. *Science* **1989**, *245*, 412.
(10) York, J. L. *J. Org. Chem.* **1981**, *46*, 2171.
(11) Holmes, R. E.; Robins, R. K. *J. Am. Chem. Soc.* **1965**, *87*, 1772.

0022-3263/90/1955-3695$02.50/0 © 1990 American Chemical Society