on a VG 7070H mass spectrometer. HPLC analyses were performed with a 6A-Shimadzu instrument with a 254-nm fixed wavelength and Chromatopac C-R3A integrator.

Methyl 2-(Sulfamoyloxy)benzoate (5a). General Procedure. To a stirred solution of methyl 2-hydroxybenzoate (3) (3.5 g, 0.023 mol) in toluene (10 mL) at 100–105 °C was added a solution of chlorosulfonyl isocyanate (2 mL, 0.023 mol) in toluene (3 mL) over a period of 10 min. Stirring was continued for 3 h at this temperature. The toluene was then removed under vacuum, and the residue obtained was added to cold water (30 mL) and left overnight. The solid was filtered, washed with water, and recrystallized from ethanol/methanol to give 4.8 g of **5a** (yield 90%): mp 87–88 °C; IR (KBr) (cm^{-1}) 3400, 3200, 1700, 1370, 1160; ^1H NMR δ 3.89 (3 H, s, OCH_3), 5.6 (2 H, br s, NH_2), 7.25–7.58 (3 H, m, aromatic H), 7.8–7.95 (1 H, dd, aromatic H). Anal. Calcd for $C_8H_9NO_5S$: C, 41.57; H, 3.92. Found: C, 41.43; H, 3.74.

4-Oxo-3,4-dihydro-1,2,3-benzoxathiazine 2,2-Dioxide (6a). General Procedure. A solution of **5a** (50 mg, 0.2 mmol) dissolved in ethanol (20 mL) and 0.02 M phosphate buffer pH 7.4 (15 mL) was added to freshly prepared microsomal suspension (5 mL). Incubation was carried out under aerobic conditions at 22–25 °C for 20 h with gentle shaking. Proteins were precipitated by the addition of acetonitrile (10 mL) to the incubation mixture. The incubation mixture was extracted two times with chloroform (25 mL). The extract was dried over Na_2SO_4 and evaporated to dryness under reduced pressure. The residue was dissolved in chloroform/methanol and was subjected to column chromatography (silica gel, chloroform/methanol, 97:3). Further recrystallization from chloroform/hexane furnished **6a** (31 mg, 74%): mp 218–220 °C dec; IR ($CHCl_3$) (cm^{-1}) 3325, 1660, 1400, 1230, 1160; ^1H NMR δ 7.23–7.85 (4 H, m, aromatic H), 13.1–13.5 (1 H, br s, NH). Anal. Calcd for $C_7H_5NO_4S$: C, 42.19; H, 2.53. Found: C, 42.26; H, 2.46.

4-Phenyl-2*H*-1,3-benzoxazin-2-one (9a). General Procedure. To 2-(carbamoyloxy)benzophenone (**8a**) (100 mg, 0.4 mmol) dissolved in ethanol (25 mL) and 0.02 M phosphate buffer pH 7.4 (20 mL) was added freshly prepared microsomal suspension (10 mL). Incubation was performed under aerobic conditions at 20–22 °C for 12 h with mild shaking. Proteins were precipitated by the addition of acetonitrile (20 mL) to the incubation mixture. The incubation mixture was extracted three times with ethyl acetate (30 mL). The organic phase was separated, and the combined organic phases were dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give the crude product **9a**, which was purified by chromatography (silica gel, chloroform/methanol, 98:2), mp 252–255 °C dec (65 mg, 71% yield): IR (KBr) (cm^{-1}) 1720, 1590. Anal. Calcd for $C_{14}H_9NO_2$: C, 75.33; H, 4.06. Found: C, 75.48; H, 3.92.

Reactions of 2-(Carbamoyloxy)- and 2-(Sulfamoyloxy)-benzoates (1 and 5) at 35–37 °C. General Procedure. These reactions were performed in a similar manner as described above at temperatures of 35–37 °C instead of 20–25 °C for 18 h. The residue obtained on workup of the reaction was charged on column chromatography (silica gel, chloroform/methanol, 98:2) to separate 2-hydroxybenzamide **10** from **2** or **6**. 2-Hydroxybenzamide **10** was further purified by recrystallization from chloroform/hexane, mp 138–140 °C, no depression in the mixed melting point and superimposable IR spectra were observed in comparison with the commercial sample of **10**. HPLC analyses showing the ratios of **10/2** and **10/6** are given in Table II.

In all the above reactions with microsomes, a control reaction was monitored under similar reaction conditions employing microsomes preheated at 80 °C for 5 min, which did not afford the products.

Preparation of Liver Microsomal Fraction from Rat. General Procedure. Livers of male Wistar strain rats, 150–220 g, fasted for 1 day before being killed, were homogenized in 0.02 M phosphate buffer (pH 7.4) containing KCl (1.15% w/v). The homogenate was centrifuged at 10000*g* for 30 min, and the resultant supernatant was further centrifuged at 105000*g* for 2 h. The microsomal pellets were resuspended in the same buffer to a final protein concentration of 5 mg/mL determined by the method of Lowry et al.[11]

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Supplementary Material Available: Physical, analytical, and ^1H NMR data for compounds **5**, **6**, and **9** (4 pages). Ordering information is given on any current masthead page.

Ti(O-*i*-Pr)$_4$-Mediated Formation of 2,3-Epithio Alcohols from 2,3-Epoxy Alcohols

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Ti(O-*i*-Pr)$_4$ facilitates the regioselective opening of 2,3-epoxy alcohols and related derivatives with a variety of nucleophiles.[1] As part of ongoing investigations into selective transformations of readily available 2,3-epoxy alcohols,[2] we studied the reaction of 2,3-epoxy alcohols with thiourea mediated by Ti(O-*i*-Pr)$_4$ and have found that good yields of homochiral trans 2,3-epithio alcohols could be obtained regio- and stereoselectively from corresponding epoxy alcohols under mild conditions. Epoxides have been transformed to episulfides by the action of thiourea in aqueous acidic solution followed by basic workup or in methanol solution.[3] Recently, homochiral *trans*-2,3-epoxy-1-hexanol was converted to homochiral *trans*-2,3-epithio-1-hexanol under the former conditions.[4] However, in this reaction a small amount of 1,2-epithio-3-hexanol was also isolated.

As shown in Scheme I, 2,3-epoxy alcohols reacted with thiourea at room temperature or 0 °C in the presence of Ti(O-*i*-Pr)$_4$ in THF. Acidic workup afforded no product from the organic phase. However, when the solution was quenched with saturated aqueous $NaHCO_3$, 2,3-epithio alcohols were obtained. The reaction proceeded with high regio- and stereoselectivity, trans-disubstituted 2,3-epoxy alcohols giving only trans 2,3-epithio alcohols with complete inversion of configuration at both stereogenic centers. The 1,2-epithio alcohols, not detected by TLC and ^1H NMR analyses, were confirmed by synthesizing the 1,2-epithio alcohols from 1,2-epoxy 3-alcohols.[4] The stereochemistry of the reaction was confirmed by correlation with the literature example.[4] For example, from (2*S*,3*S*)-2,3-epoxy-1-hexanol (~94% ee) the corresponding (2*R*,3*R*)-2,3-epithio-1-hexanol (**3a**) (~94% ee) was obtained without loss of enantiomeric excess, which was confirmed by ^1H NMR analysis of the ester derived from (+)-MTPA chloride. In general, trans 2,3-epoxy alcohols gave good yields; however, with cis 2,3-epoxy alcohols the yields were low and thio diols were also formed. Epithiocinnamyl alcohols could also be prepared from the

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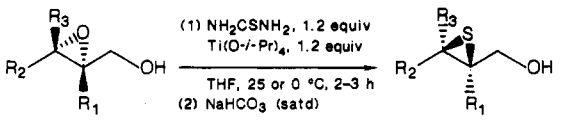
0022-3263/88/1953-4114$01.50/0

Scheme I. Synthesis of Epithio Alcohols from Epoxy Alcohols



epithio alc	R_1	R_2	R_3	temp, °C	yield,[a] %	config[c]
1	H	n-C_8H_{17}	H	25	69–90	2*R*,3*R*
2	H	n-C_5H_{11}	H	25	82	2*R*,3*R*
3a	H	n-C_3H_7	H	25	64	2*R*,3*R*
3b	H	n-C_3H_7	H	25	69	2*S*,3*S*
4	H	c-C_6H_{11}	H	25	77	2*R*,3*R*
5	H	H	CH_2OCH_2Ph	25	50	2*R*,3*S*
6	H	H	n-C_8H_{17}	25	30	2*R*,3*S*
7	n-$C_{14}H_{29}$	H	H	0	42	racemic
8	H	Ph	H	0	66[b]	2*R*,3*R*
9	H	p-BrC_6H_4	H	0	73[b]	2*S*,3*S*

[a] Yields reported are isolated yields. [b] Decomposes on standing. [c] See ref 4.

corresponding epoxycinnamyl alcohols at low temperature (0 °C). However, they were found to decompose to cinnamyl alcohols and sulfur on standing. Without Ti(O-*i*-Pr)$_4$, thiourea was insoluble in THF and the reaction did not proceed. One equivalent of Ti(O-*i*-Pr)$_4$ was required to achieve completion of the reaction, and THF was the best solvent (reaction did not proceed in ether, CH_2Cl_2, or benzene under similar conditions).

In conclusion, this method provides a mild and selective synthesis of homochiral trans 2,3-epithio alcohols from readily available chiral trans 2,3-epoxy alcohols.[2]

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR spectra were measured at 250 MHz. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter with a 1-cm^3 capacity (10-cm path length) quartz cell.

Ti(O-*i*-Pr)$_4$ was distilled and stored under an inert atmosphere. Tetrahydrofuran was distilled from sodium benzophenone ketyl and stored over activated 3A molecular sieves. Thiourea was reagent grade (>99% purity) and used as received. Flash chromatography was performed with Merck silica gel 60 (230–400 mesh) as described by Still.[5] Homochiral epoxy alcohols were prepared by catalytic asymmetric epoxidation.[2] Racemic epoxy alcohols were prepared by using TBHP and VO(acac)$_2$.[6] Enantiomeric excesses of the epoxy and epithio alcohols were determined by ^{1}H NMR analysis of the ester derived from (+)-MTPA chloride. These analyses were performed in C_6D_6 at 250 MHz, focusing on the terminal methylene protons, which were observed as a diastereomeric pair of AB doublets (dd) around δ 4.0.[2] The following 2,3-epoxy alcohols were used (enantiomeric excesses in parentheses): (−)-(2*S*,3*S*)-2,3-epoxy-1-undecanol (>98% ee); (−)-(2*S*,3*S*)-2,3-epoxy-1-octanol (98% ee); (−)-(2*S*,3*S*)-2,3-epoxy-1-hexanol (94% ee); (+)-(2*R*,3*R*)-2,3-epoxy-1-hexanol (90% ee); (−)-(2*S*,3*S*)-2,3-epoxy-3-cyclohexyl-1-propanol (96% ee); (−)-(2*S*,3*R*)-2,3-epoxy-4-(benzyloxy)-1-butanol (90% ee); (−)-(2*S*,3*R*)-2,3-epoxy-1-undecanol (80% ee); 2,3-epoxy-2-tetradecyl-1-propanol (racemic); (−)-(2*S*,3*S*)-2,3-epoxycinnamyl alcohol (>98% ee); (+)-(2*R*,3*R*)-2,3-epoxy-4-bromocinnamyl alcohol (>98% ee).

General Procedure. Preparation of (2*R*,3*R*)-2,3-Epithio-1-undecanol (1). To a suspension of (2*S*,3*S*)-2,3-epoxy-1-undecanol (0.47 g, 2.5 mmol, >98% ee) and thiourea (0.23 g, 3.0 mmol) in 15 mL of THF was added Ti(O-*i*-Pr)$_4$ (0.91 mL, 3.0 mmol) at room temperature under nitrogen. After addition, the thiourea gradually dissolved and a clear solution formed which was stirred for 2 h. The solution was then diluted with 10 mL of ether and quenched with 5 mL of saturated aqueous $NaHCO_3$ solution. The resulting mixture was stirred vigorously for ca. 1 h as a white precipitate separated from solution. The mixture was filtered through a pad of Celite, and the residue was washed thoroughly with 20 mL of ether and then 20 mL of CH_2Cl_2. The combined organic phases were then washed with water (2 × 10 mL) and saturated brine (10 mL) and dried over $MgSO_4$. After concentration, the crude product was purified on silica gel (eluting with 35% ethyl acetate in hexane) to afford (2*R*,3*R*)-2,3-epithio-1-undecanol (1) as a white solid (0.46 g, 90% yield, >98% ee by ^{1}H NMR analysis of the ester derived from (+)-MTPA chloride): mp 39–40 °C; $[\alpha]^{23}_D$ +119.7° (*c* 2.35, $CHCl_3$); IR (Nujol) 3350, 2920, 2850, 1450, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.85–3.95 (m, 1), 3.75–3.85 (m, 1 H), 3.02 (ddd, *J* = 4.5, 4.7, 4.9 Hz, 1 H), 2.83–2.90 (m, 1 H), 1.70–1.90 (m, 2 H), 1.40–1.60 (m, 3 H), 1.20–1.45 (m, 10 H), 0.90 (t, *J* = 7.0 Hz, 3 H). Anal. Calcd for $C_{11}H_{22}OS$: C, 65.29; H, 10.96; S, 15.84. Found: C, 64.95; H, 10.83; S, 15.59.

The following compounds were prepared in a manner similar to 1, except compounds 7, 8, and 9, which were prepared at 0 °C instead of room temperature.

(2*R*,3*R*)-2,3-Epithio-1-octanol (2): as a colorless oil; $[\alpha]^{23}_D$ +154.0° (*c* 2.48, $CHCl_3$); ~98% ee; IR (film) 3235, 2960, 2920, 2850, 1450, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.85–3.95 (m, 1 H), 3.65–3.75 (m, 1 H), 2.95 (ddd, *J* = 4.6, 4.7, 5.0 Hz, 1 H), 2.77–2.82 (m, 1 H), 1.75–1.90 (m, 1 H), 1.40–1.60 (m, 3 H), 1.25–1.40 (m, 4 H), 0.90 (t, *J* = 7.0 Hz, 3 H). Anal. Calcd for $C_8H_{16}OS$: C, 59.95; H, 10.06; S, 20.0. Found: C, 60.07; H, 10.32; S, 19.79.

(2*R*,3*R*)-2,3-Epithio-1-hexanol (3a): as a colorless oil; $[\alpha]^{23}_D$ +159.2° (*c* 3.51, $CHCl_3$); (lit.[4] $[\alpha]^{20}_D$ +153.3° [*c* 1.18, $CHCl_3$]); ~94% ee; ^{1}H NMR ($CDCl_3$) δ 3.85–3.95 (m, 1 H), 3.65–3.75 (m, 1 H), 2.95 (ddd, *J* = 4.6, 4.7, 4.9 Hz, 1 H), 2.78–2.85 (m, 1 H), 1.70–1.90 (m, 2 H), 1.45–1.65 (m, 3 H), 1.0 (t, *J* = 7.0 Hz, 3 H).

(2*S*,3*S*)-2,3-Epthio-1-hexanol (3b): as a colorless oil; $[\alpha]^{23}_D$ −140.8° (*c*, 3.00, $CHCl_3$); (lit.[4] $[\alpha]^{20}_D$ −144.2°).

(2*R*,3*R*)-2,3-Epithio-3-cyclohexyl-1-propanol (4): as a colorless oil; $[\alpha]^{23}_D$ +137.0° (*c* 3.28, $CHCl_3$); ~96% ee; IR (film) 3335, 2920, 2850, 1450, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.85–3.95 (m, 1 H), 3.60–3.75 (m, 1 H), 2.95 (ddd, *J* = 4.8, 4.8, 5.0 Hz, 1 H), 2.61 (ddd, *J* = 2.7, 5.4, 5.4 Hz, 1 H), 1.60–1.90 (m, 6 H), 1.00–1.35 (m, 6 H).

(2*R*,3*S*)-2,3-Epithio-4-(benzyloxy)-1-butanol (5): as a colorless oil; $[\alpha]^{23}_D$ +27.42° (*c* 2.67, $CHCl_3$); IR (film) 3400, 2850, 1450, 1360, 1200, 1050, 750, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35 (bs, 5 H), 4.50–4.70 (m, 2 H), 3.95–4.15 (m, 2 H), 3.40–3.60 (m, 2 H), 3.15–3.25 (m, 2 H), 2.90–3.10 (m, 1 H). Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71; S, 15.25. Found: C, 62.72; H, 6.85; S, 15.13.

(2*R*,3*S*)-2,3-Epithio-1-undecanol (6): as a colorless oil; $[\alpha]^{23}_D$ −21.94° (*c*, 2.94, $CHCl_3$); IR (film) 3350, 2920, 2850, 1450, 1030 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.76–3.98 (m, 2 H), 3.22 (ddd, *J* = 6.5, 6.5, 6.7 Hz, 1 H), 2.98–3.08 (m, 1 H), 1.80–2.00 (m, 1 H), 1.50–1.70 (m, 4 H), 1.20–1.45 (m, 10 H), 0.90 (t, *J* = 7.1 Hz, 3 H).

***rac*-2,3-Epithio-2-tetradecyl-1-propanol (7):** as a colorless oil; IR (film) 3400, 2920, 2860, 1460, 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.81 (dd, *J* = 4.1, 15.8 Hz, 1 H), 3.71 (dd, *J* = 8.9 Hz, 1 H), 2.55 (s, 1 H), 2.33 (d, *J* = 0.93 Hz, 1 H), 1.75–1.95 (m, 2 H), 1.40–1.50 (m, 2 H), 1.25 (m, 23 H), 0.88 (t, *J* = 7.0 Hz, 3 H).

(2*S*,3*S*)-2,3-Epithio-4-bromocinnamyl alcohol (9): ^{1}H NMR ($CDCl_3$) δ 7.45 (d, *J* = 7.0 Hz, 2 H), 7.15 (d, *J* = 7.0 Hz, 2 H), 3.95–4.05 (m, 1 H), 3.85–3.95 (m, 1 H), 3.80 (d, *J* = 6.5 Hz, 1 H),

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3.30–3.40 (m, 1 H), 1.85–1.95 (m, 1 H).

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Registry No. 1, 115290-82-9; 2, 115290-83-0; 3a, 92610-81-6; 3b, 92693-35-1; 4, 115290-84-1; 5, 115290-85-2; 6, 115362-11-3; 7, 115290-86-3; 8, 115290-87-4; 9, 115290-88-5; $Ti(O\text{-}i\text{-}Pr)_4$, 546-68-9; (-)-(2S,3S)-2,3-epoxy-1-undecanol, 101976-99-2; (-)-(2S,3S)-2,3-epoxy-1-octanol, 89461-51-8; (-)-(2S,3R)-2,3-epoxy-1-hexanol, 89321-71-1; (+)-(2S,3R)-2,3-epoxy-1-hexanol, 92418-71-8; (-)-(2R,3R)-2,3-epoxy-1-cyclohexyl-1-propanol, 115362-12-4; (-)-(2S,3R)-2,3-epoxy-4-(benzyloxy)-1-butanol, 78513-07-2; (-)-(2S,3R)-2,3-epoxy-1-undecanol, 96249-61-5; 2,3-epoxy-2-tetradecyl-1-propanol, 88393-68-4; (-)-(2S,3S)-2,3-epoxycinnamyl alcohol, 104196-23-8; (+)-(2R,3R)-2,3-epoxy-4-bromocinnamyl alcohol, 115362-13-5.

New Maytansinoids: Reduction Products of the C(9) Carbinolamide

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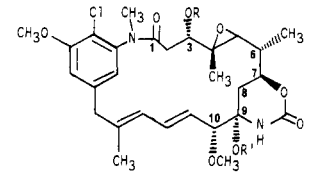
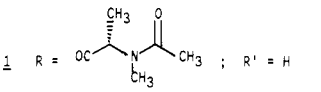
Ongoing research in our laboratory has been directed toward the preparation of derivatives of the maytansinoids, a class of naturally occurring potent antileukemic agents exemplified by maytansine (1).[1-4] In particular, we have focused our attention upon derivatives of the C3 and C9 positions. In the course of selecting a reducing agent for the efficient formation of maytansinol (2) from maytanbutine (3), one reagent, lithium borohydride in the presence of 10% lithium triethylborohydride,[5] was found to give a product, maytancarbutine[6] (4), that was modified only in the region of the C9 carbinolamide. Maysine (5), which lacks the C3 ester side chain, was reacted under the same conditions to give an analogous product, maycarsine[6] (6). Reactions of the borohydride reagent with a model compound 7 and the C9 methyl ether of maytanbutine (8) suggested a mechanism that involves hydrolysis of the carbinolamide followed by hydride addition to an intermediate ketone at C9.

In a typical reaction for the formation of 4, 3 was reduced with 10 equiv of lithium borohydride and 1 equiv of lithium triethylborohydride over the course of 36 h in THF. After workup, a 66% yield of 4 was obtained. In addition, a 20% yield of 6 was obtained and 5% of 3 was recovered. The product 4 was also obtained upon reaction of 3 with only lithium borohydride. However, yields were significantly lower and longer reaction times were required.

Microanalysis, the FAB mass spectrum, and the high-resolution electron-impact mass spectrum of 4 suggested a molecular formula of $C_{36}H_{52}ClN_3O_{10}$, which was consistent with a simple reduction of 3. In the HREIMS of 4, no ion was observed at m/z 658 ($[M - HNCO - H_2O]^+$) or m/z 485 as would be expected from a normal maytansinoid.[7] However, a significant ion was observed at m/z 678.3264 (3.86%, $C_{35}H_{51}ClN_2O_9$), indicative of a loss of only HNCO from the molecular ion of 4. Subsequent loss of the C3 ester gave an ion at m/z 505.2155. These data suggested that reduction of the carbinolamide of 3 had occurred to give 4 in which the C9-OH was less susceptible to elimination in the mass spectrometer.





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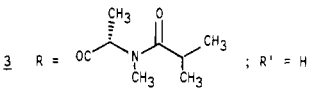

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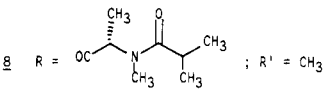

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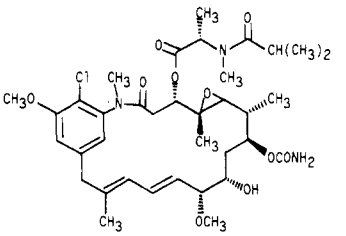

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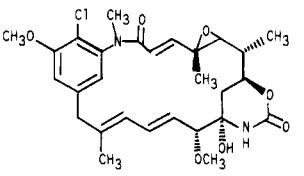

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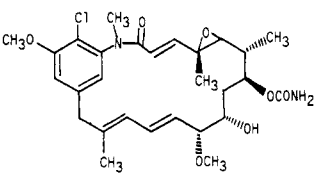

6

The ^1H NMR data for 4 also suggested that the borohydride mixture reacted selectively with the C9 carbinolamide of 3. The ^1H NMR spectra of 4 differed most notably from the spectra of 3 (Table I) in the absence of the C9-NH resonance and the presence of a new, two-proton singlet at 4.90 ppm, which shifted to 7.30 ppm when the spectrum was measured in acetone-d_6, and a new, one-proton doublet at 3.85 ppm. These data suggested that the carbinolamide ring had cleaved to give a carbamoyl group at C7 and a secondary hydroxyl group at C9. This conclusion was supported by the downfield shift of the C7-H multiplet and the upfield shifts of the resonances for C6-H, C6-CH_3, C10-H, and C10-OCH_3. The C10-H appeared as a doublet of doublets, confirming the presence of a hydrogen at C9. Additional evidence for the proton at C9 was found in the ^{13}C NMR spectrum of 4. A doublet

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(6) The trivial names for 4 and 6 were derived from the trivial names for the parent compounds 3 and 5 and are meant to imply the presence of the carbamoyl group at C7.

(7) The electron-impact mass spectra of maytansinoids bearing C3 esters typically do not show parent ions. Instead, an immediate loss of (HNCO + H_2O) resulting from the fragmentation of the carbinolamide gives an ion observed at $M^+ - 61$. Subsequent elimination of the C3 ester of maytansinoids then results in an ion at m/z 485.[1]

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