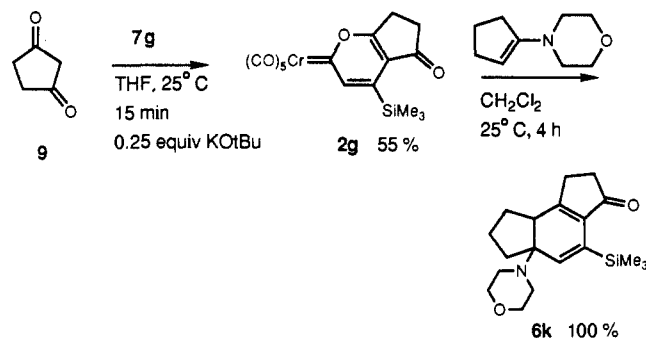


**4c** resulted only in the formation of the aromatized product **3c**. Also illustrated in this example is the expected rate enhancement<sup>1b,2</sup> of the pyranilidene complexes. Complex **2d** reacts with ethyl vinyl ether at room temperature (entry 4), whereas the  $\alpha$ -pyrone **1c** requires an elevated temperature (78 °C) over a longer period of time. As indicated by the preparation of **6k**, these



reactions can be extended to pyranilidene complexes prepared from cyclic dicarbonyl compounds. The ketene acetal derived products **6i** and **6j** are produced in high yields and can be obtained relatively pure as crude products since the chromium carbonyl side product can be removed under vacuum. Although these products can be characterized in this form, any attempts to purify them by silica gel chromatography or distillation result in aromatization. Phenol acetals of this type have been reported in only a few limited occasions, and pyranilidene complexes offer a clean method for their generation.<sup>3m,8</sup>

The inverse-electron-demand Diels-Alder reactions of pyranilidene complexes give dihydrobenzene products and complement the reactions of  $\alpha$ -pyrones where aromatic products are typically produced, and accordingly, synthetic applications of these reactions are to be expected.

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**Supplementary Material Available:** Spectral data for all new compounds (6 pages). Ordering information is given on any current masthead page.

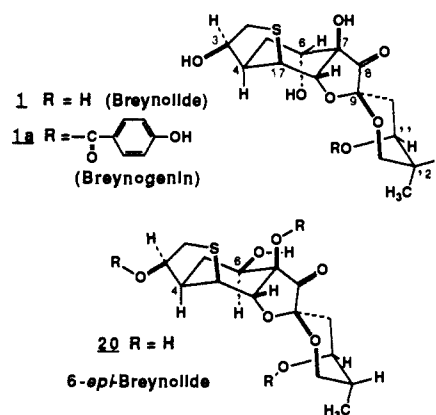
## Total Synthesis of (+)-Breynolide

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Breynin A and B are novel sulfur-containing glycosides isolated from *Breynia officinalis* Hemsl,<sup>1</sup> which have displayed remarkable hypocholesterolemic activity in rats at daily oral doses of 0.005 mg/kg and 0.025 mg/kg, respectively. Investigators at the Bristol-Banyu Research Institute have characterized (+)-breynogenin (**1a**) and (+)-breynolide (**1**) as the aglycon hydrolysis products of these antibiotic disaccharides. Stereochemical features and the absolute configuration of (+)-breynolide (**1**) have been unambiguously determined by X-ray crystallography,<sup>2</sup> revealing a unique perhydrobenzothiophene as part of a highly oxygenated polycyclic nucleus. The 1,6-dioxaspiro[5.4]ketal is structurally similar to that component as found in (+)-phyllanthocin, the aglycon of a family of potent antineoplastic agents.<sup>3</sup> Herein we report the first total synthesis of optically active (+)-breynolide.



From the onset of our investigations, we had sought to develop an efficient convergent strategy that would introduce the thioether (position 1 of breynolide) after the necessary oxygenations of a carbon framework. All of these hydroxy and alkoxy substituents are disposed as axial or pseudoaxial within their respective ring systems. Secondly, the presence of the  $\beta$ -hydroxy ketone of **1** ( $C_6 \rightarrow C_8$ ) suggested that an aldol condensation could be adopted for construction of the cyclohexane ring in the final stages. Thus, the 1,6-dioxaspiro[5.4]decanone could be assembled from a highly oxygenated acyclic backbone with completion of the natural product via closure of the only carbocyclic ring of the molecule.<sup>4</sup>

An aldehydic subunit representing  $C_7-C_{13}$  of breynolide (**1**) allowed masking of the  $C_9$  ketone by internal participation of the  $C_{13}$  alcohol as a mixed ketal **2**. This material was prepared as shown in Scheme 1, starting with monoprotected 4(*S*)-methyl-2-pentene-1,5-diol **3**, which was readily supplied via modifications of literature procedures from (-)-methyl 3-hydroxy-2(*R*)-methylpropionate.<sup>6</sup> Mosher esters of allylic alcohol **3** showed

(1) Sasaki, F.; Ohkuma, H.; Naito, T.; Kawaguchi, H. *Chem. Pharm. Bull.* 1976, 24, 114. Koshiyama, H.; Hatori, M.; Ohkuma, H.; Sasaki, F.; Imanishi, H.; Ohbayashi, M.; Kawaguchi, H. *Ibid.* 1976, 24, 169.

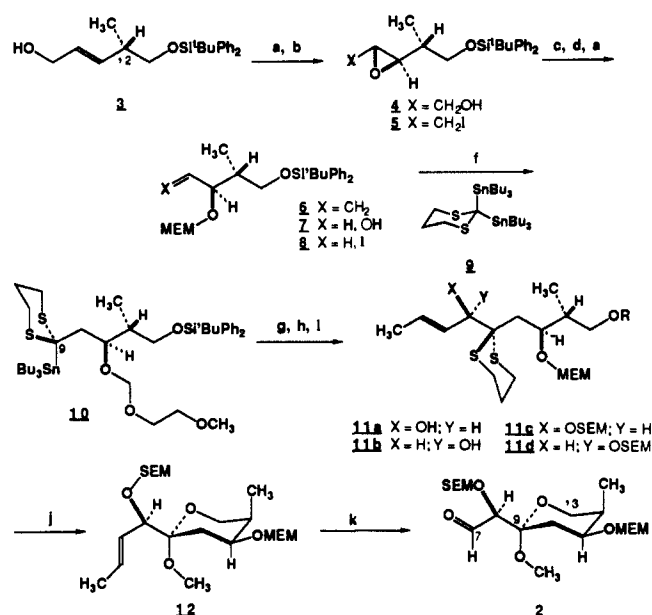
(2) Sasaki, K.; Hirata, Y. *Tetrahedron Lett.* 1973, 2439.

(3) Pettit, G. R.; Cragg, G. M.; Gust, D.; Brown, P. *Can. J. Chem.* 1982, 60, 544. Interest in (+)-breynolide originated from our previous efforts toward 1,6-dioxaspiro[5.4]ketals in our total synthesis of (+)-phyllanthocin. See: Williams, D. R.; Sit, S.-Y. *J. Am. Chem. Soc.* 1984, 106, 2949. For related synthetic studies of (+)-phyllanthoside, see: Smith, A. B.; Rivero, R. A. *J. Am. Chem. Soc.* 1987, 109, 1272 and references therein.

(4) For an approach toward breynolide, see: Nishiyama, S.; Ikeda, Y.; Yoshida, S.-I. *Tetrahedron Lett.* 1989, 30, 105.

(5) Footnote deleted on revision.

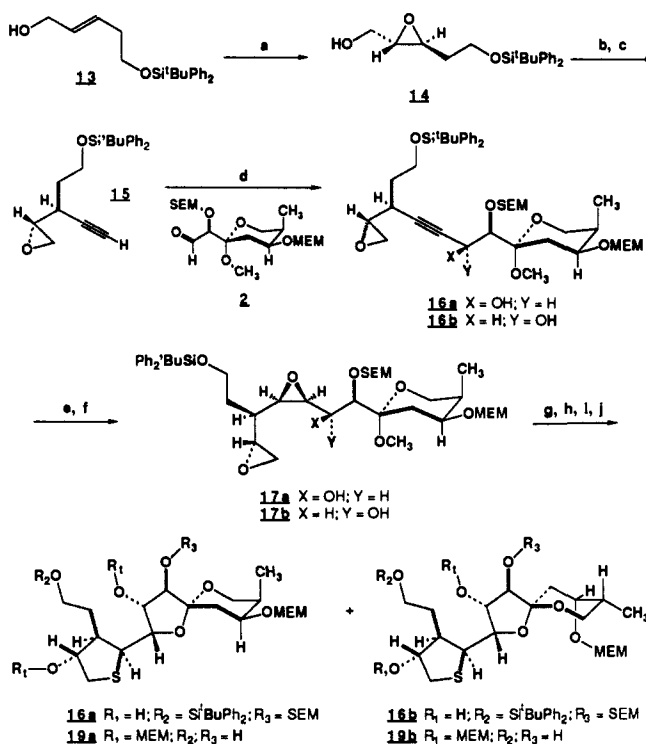
(8) (a) Atkinson, R. S.; Gawad, N. A. *J. Chem. Soc., Perkin Trans. 1* 1985, 825. (b) Atkinson, R. S.; Fawcett, J.; Gawad, J.; Nagwa, A.; Russell, D. R.; Sherry, L. J. *S. J. Chem. Soc. Chem. Commun.* 1984, 1072. (c) Russell, R. A.; Evans, D. A. C.; Warriner, R. N. *Aust. J. Chem.* 1984, 37, 1699. (d) Kurosawa, K.; Takamura, T.; Ueno, Y.; McOmie, J. F.; Pearson, N. D. *Bull. Chem. Soc. Jpn.* 1984, 57, 1914. (e) Spangler, L. A.; Swenton, J. S. *J. Org. Chem.* 1984, 49, 1800. (f) Chenard, B. L.; Dolson, M. G.; Sercel, A. D.; Swenton, J. S. *J. Org. Chem.* 1984, 49, 318. (g) Kikuchi, Y.; Hasegawa, Y.; Matsumoto, M. *J. Chem. Soc., Chem. Commun.* 1982, 878. (h) Chenard, B. L.; Anderson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* 1980, 932.

Scheme I.<sup>a</sup> Synthesis of the C<sub>7</sub> → C<sub>13</sub> Segment 2

<sup>a</sup>(a) D-DET (0.13 equiv); Ti(O<sup>i</sup>Pr)<sub>4</sub> (0.10 equiv); <sup>t</sup>BuOOH (1.8 equiv); 4-Å sieves; CH<sub>2</sub>Cl<sub>2</sub> at -20 °C; 32 h (96%). (b) Ph<sub>3</sub>P (1.05 equiv); I<sub>2</sub> (1.02 equiv); imidazole (1.3 equiv); CH<sub>2</sub>Cl<sub>2</sub> at 0 °C → reflux; 1 h (95%). (c) <sup>t</sup>BuLi (2.2 equiv); Et<sub>2</sub>O at -78 °C; 15 min, then MEM-Cl; <sup>t</sup>Pr<sub>3</sub>N-Et; Et<sub>2</sub>O; CH<sub>2</sub>Cl<sub>2</sub> at 0 °C → room temperature; 16 h (94%). (d) Excess O<sub>3</sub>; MeOH (1.0 equiv); CH<sub>2</sub>Cl<sub>2</sub> at -78 °C, then MeOH (2 equiv); NaBH<sub>4</sub> (3 equiv); -78 °C → room temperature; 6 h, (93%). (e) Repeat step b; reflux 6 h (94%). (f) **13** (1.20 equiv); <sup>n</sup>BuLi (1.18 equiv); THF at -78 °C; 1 h, then **12** in THF at -78 °C; 2 h (83%). (g) <sup>n</sup>BuLi; THF at -78 °C; 1 h, then 2-butenal; 15 min (97%). (h) KH (1.2 equiv); THF at 0 °C; 1 h, then SEM-Cl (1.5 equiv); 0 °C → room temperature; 1 h, (87%). (i) <sup>n</sup>Bu<sub>4</sub>NF, (1.5 equiv); THF; room temperature, 4 h (98%). (j) NBS (3.0 equiv) collidine (2.0 equiv); MeOH; MeCN (1:1) at room temperature; 10 min, then saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>, then saturated CuSO<sub>4</sub>, then TsOH (0.05 equiv); MeOH at 0 °C; 5 min (80%). (k) Excess O<sub>3</sub>; CH<sub>2</sub>Cl<sub>2</sub> at -78 °C, then Ph<sub>3</sub>P; -78 °C → room temperature; 90 min (95%).

no trace of racemization at C<sub>12</sub> (<2%). Asymmetric Sharpless epoxidation under catalytic conditions provided nearly quantitative conversion to oxirane **4** in high diastereomeric purity (de >95%).<sup>7</sup> Rapid addition of *tert*-butyllithium in pentane afforded an instantaneous reductive elimination of the crystalline iodide **5** (mp 52–53 °C), and subsequent introduction of (2-methoxyethoxy)-methyl chloride led directly to isolation of the allylic ether **6**. Slow addition of a solution of excess ozone provided oxidative cleavage of the terminal alkene **6**, and a reductive quench with sodium borohydride yielded primary alcohol **7**.

An alkylation sequence was employed to introduce C<sub>9</sub> as an effective acyl anion equivalent. This was expeditiously accomplished by stepwise lithiations of 2,2-bis(tri-*n*-butylstannyl)-1,3-dithiane as pioneered by Seebach.<sup>8</sup> Pretreatment of **9** with *n*-butyllithium at -78 °C, and facile alkylation at -78 °C using the rather unreactive primary iodide **8**, afforded organostannane **10** (62% overall yield from **3**). Repetitive lithiation<sup>9</sup> and alkylation of **10** with freshly distilled 2-butenal provided a 97% yield of diastereomeric

Scheme II.<sup>a</sup>

<sup>a</sup>(a) L-DET (0.08 equiv); Ti(O<sup>i</sup>Pr)<sub>4</sub> (0.06 equiv); <sup>t</sup>BuOOH (1.5 equiv); 4-Å sieves; CH<sub>2</sub>Cl<sub>2</sub> at -20 °C; 20 h (85%). (b) Me<sub>2</sub>AlC≡CH·Et<sub>2</sub>O (2.5 equiv, 2 M in toluene); hexanes at 0 °C → room temperature (65%). (c) TsCl (1.0 equiv); Et<sub>3</sub>N (1.5 equiv); CH<sub>2</sub>Cl<sub>2</sub> at 0 °C; 24 h, then Triton B (1.5 equiv, 40% in MeOH); room temperature; 2 h (69%). (d) **20** (1.5 equiv); <sup>t</sup>BuLi (1.2 equiv); THF at -78 °C; 1 h; then **6** (1.0 equiv) in THF; -95 °C → -78 °C; 20 min; then HOAc (1.6 equiv → room temperature) (85%). (e) H<sub>2</sub>; Pd-CaCO<sub>3</sub>/Pb (20% by weight); EtOAc at room temperature; 8 h (89%). (f) *m*-CPBA (1.8 equiv); NaHCO<sub>3</sub> (5 equiv); CH<sub>2</sub>Cl<sub>2</sub> at room temperature; 10 h (97%). (g) NaSH·XH<sub>2</sub>O (20% by weight); EtOH at room temperature; 2 h (88%). (h) TsOH (0.10 equiv); CH<sub>2</sub>Cl<sub>2</sub> at -20 °C; 1 h (88%). (i) KH (3.0 equiv); THF at 0 °C; 90 min, then MEM-Cl (2.5 equiv); 15 min (91%). (j) <sup>n</sup>Bu<sub>4</sub>NF (~2 M) in THF (5 equiv); 45 °C; 4 h (85%).

allylic alcohols **11a** and **11b** (R = Si<sup>t</sup>BuPh<sub>2</sub>; 3:1 ratio, respectively).<sup>10</sup> Chromatographic separation of these alcohols led to protection of each as their corresponding [2-(trimethylsilyl)ethoxy]methyl (SEM) ethers.<sup>11</sup> Ketal exchange of the dithiane unit of **11c** (R = H) was clearly achieved by using excess *N*-bromosuccinimide in methanol-acetonitrile in the presence of dry collidine. The overall success of this transformation was acutely dependent upon the proportion of collidine and reaction times. Upon quenching with aqueous sodium thiosulfate, the crude reaction product<sup>12</sup> was washed with aqueous CuSO<sub>4</sub> and dissolved in acidic methanol, affording the purified ketal **12** ([α]<sub>D</sub><sup>25</sup> -71°; *c* = 3.00, CHCl<sub>3</sub>), as the result of thermodynamic product development. Finally, ozonolysis of **12** at -78 °C provided excellent conversion to the C<sub>7</sub> → C<sub>13</sub> component **2**.

The carbon fragment containing C<sub>2</sub> → C<sub>16</sub> was readily obtained and combined with aldehyde **2** as illustrated in Scheme II. The necessary asymmetry was secured by Sharpless epoxidation giving the optically active oxirane **14**.<sup>13</sup> Regiocontrolled addition of

(6) Evans, D. A.; Sacks, C. E.; Kleschick, W. A.; Taber, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 6789. Silylation and lithium borohydride reduction were followed by Swern oxidation at -78 °C with in situ addition of methyl (triphenylphosphoranylidene)acetate at -78 °C with warming to -10 °C, producing an 87% yield of separable α,β-unsaturated methyl esters (*E*:*Z* ratio is 95:5). See: Ireland, R.; Norbeck, D. *J. Org. Chem.* **1985**, *50*, 2198. Finally, reduction (DIBAL; -78 °C) gave the required 2-penten-1-ol.

(7) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(8) Seebach, D.; Willert, I.; Beck, A.; Groebel, B.-T. *Helv. Chim. Acta* **1978**, *61*, 2510.

(9) A significant advantage of the (tri-*n*-butylstannyl)dithiane **10** is the relative ease of transmetalation versus deprotonation of the corresponding C<sub>2</sub>-H dithiane as experienced in our phyllanthocin synthesis (ref 3b).

(10) Either alcohol epimer **11ab** was effectively interconverted into the other upon DDQ oxidation (CH<sub>2</sub>Cl<sub>2</sub>; 22 °C; 80%) yielding an enone for subsequent hydride reduction (NaBH<sub>4</sub>; CeCl<sub>3</sub>; MeOH; -20 °C; 83%).

(11) For clarity, we have illustrated our synthetic scheme from the major diastereoisomer **11a**. However, asymmetry at C<sub>3</sub> is not present in breynolide itself. Further utilization of isomer **11d** will be presented in the full account of this work.

(12) We avoided longer reaction times and additional collidine, which promoted some epimerization at C<sub>9</sub>, presumably through an intermediate vinyl thioether. The crude product of NBS ketal exchange was a mix of C<sub>9</sub> ketone, dimethyl ketals, and hemiketals.

(13) Mosher ester derivation of **14** reveals >95% ee. See ref 7.

ethynylaluminum diethyl ether complex,<sup>14</sup> prepared as a 2 M solution in toluene, afforded a 65% isolated yield of a 1,2-diol, which was efficiently converted into the corresponding terminal epoxide **15** in a single reaction by initial treatment with *p*-toluenesulfonyl chloride followed by quenching with a methanolic solution of Triton B. Deprotonation of **15** at -78 °C resulted in a well-behaved acetylide, and condensations with **2** were extremely stereoselective, affording propargylic alcohol **16a** via an  $\alpha$ -chelation-controlled addition (75:1 ratio). Hydrogenation to the Z-allylic alcohol and oxidation provided our key intermediate **17**. Although our epoxidation was nearly quantitative, the  $\beta$ -oxirane **17a** (57% isolated yield) was a result of the Henbest directive effects of a neighboring allylic  $\beta$ -alcohol at C<sub>7</sub> in spite of considerable steric factors, which also promoted formation of undesired  $\alpha$ -epoxide.<sup>15</sup>

The three heterocyclic rings of breynolide were established from our acyclic precursor **17** as initiated by nucleophilic attack of sodium hydrogen sulfide. Initial opening of the terminal oxirane directed an intramolecular backside displacement at C<sub>17</sub> with formation of the tetrahydrothiophene nucleus. Further treatment with *p*-toluenesulfonic acid spontaneously effected a kinetic spiroketalization, affording an 88% yield of 1,6-dioxaspiro[5.4]-ketals **18a** and **18b** in a 1:3 ratio.<sup>16</sup> Each spiro ether was independently converted to the natural product via a five-step sequence. Protection of the diols as their MEM ethers and subsequent desilylation gave our penultimate precursor **19**, which upon Swern oxidation at -78 °C provoked an immediate intramolecular aldol upon addition of triethylamine at -78 °C with warming to -60 °C.<sup>17</sup> This led to a 90% isolated yield of a single keto alcohol **20** (R = MEM). Subsequent deprotection of **20** afforded a crystalline tetrol, (C<sub>6</sub>-*epi*-breynolide), **20** (R = H), mp 218–221 °C (EtOAc). Our decoupling studies suggested that **20** was the undesired diastereomeric equatorial alcohol at C<sub>6</sub>, as later confirmed by X-ray crystallography.<sup>18</sup> Finally, the total synthesis of **1** was completed by Mitsunobu inversion<sup>19</sup> with aqueous sodium formate in tetrahydrofuran at 0 °C (92%). Deprotection using aqueous hydrobromic acid (THF; room temperature; 72 h, 74%) slowly hydrolyzed each of the three MEM ethers, yielding fine white crystalline needles of (+)-breynolide, mp 241–243 °C (EtOAc), as confirmed by X-ray diffraction of our synthetic material.<sup>20</sup>

**Acknowledgment.** We thank the National Institutes of Health (AI17668), the National Science Foundation (CHE8618955), and

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(15) The Henbest oxidation often provides excellent hydrogen-bonded directivity for Z-allylic alcohols. Narula, A. S. *Tetrahedron Lett.* **1983**, *24*, 5421. Kishi, Y.; Hasan, I. *Ibid.* **1980**, *21*, 4229 and references therein. A detailed study of epoxidation reactions within the series of Z-allylic alcohols from **16ab** will be described in the full account.

(16) Prolonged acid treatment at warmer temperatures (0 °C) led to substantial decomposition of **18b**. The series of compounds bearing the unnatural C<sub>9</sub> spiroketal configuration is characteristically recognized by the chemical shift of its axial methyl (**18a**:  $\delta = 1.02$ ), whereas the natural diastereomer configurations display the methyl significantly upfield (**18b**:  $\delta = 0.91$ ).

(17) For previous studies of our intramolecular aldol condensations, see: Williams, D. R.; Klingler, F. D. *J. Org. Chem.* **1988**, *53*, 2134. Williams, D. R.; Klingler, F. D.; Dabral, V. *Tetrahedron Lett.* **1988**, *29*, 3415.

(18) Structure assignment of 6-*epi*-breynolide was unambiguously confirmed by a single-crystal X-ray diffraction study (at -155 °C). All atoms, including hydrogens, were located. Complete crystallographic data are available from the Indiana University Chemistry Library. Request Molecular Structure Center Report 89165. Spiroketal diastereomers at C<sub>9</sub> of **20** are isomerized to the natural configuration in the final deprotection with HBr.

(19) Mitsunobu, O. *Synthesis* **1981**, 1.

(20) We gratefully acknowledge Dr. Yoshio Abe, Bristol-Myers Research Institute, Tokyo, for his help in obtaining an authentic sample of breynin A for <sup>1</sup>H NMR comparisons. Structure assignment of our synthetic (+)-breynolide was unambiguously confirmed by a single-crystal X-ray diffraction (at -172 °C). All atoms, including hydrogens, were located, and diffraction data was directly compared with results for natural material. Complete crystallographic data are available from the Indiana University Chemistry Library. Request Molecular Structure Center Report 90070.

the Indiana Affiliates of the American Heart Association for their financial support of this research.

**Supplementary Material Available:** IR, NMR, and HRMS data for key substances (9 pages). Ordering information is given on any current masthead page.

### Characterization of the in Vitro Cyclization Chemistry of Calicheamicin and Its Relation to DNA Cleavage

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At dramatically low concentrations in the presence of thiols, calicheamicin  $\gamma_1^1$  (**1**)<sup>1,2</sup> shares with the esperamicins<sup>3,4</sup> and the neocarzinostatin chromophore<sup>5</sup> the ability to cause single- and, notably with the former, double-strand cleavages of DNA. The mechanism of DNA scission has been proposed<sup>1</sup> to involve four steps (Scheme I): (1) bioreductive cleavage (e.g., by reaction with glutathione in vivo) of the allylic methyl trisulfide of **1**, (2)  $\beta$ -addition of the resulting thiol to the enone to form dihydrothiophene **2**, (3) cyclization of **2** to generate a 1,4-diy<sup>6</sup> **3** that, when bound in the minor groove of DNA,<sup>2</sup> is hypothesized to abstract a hydrogen from the deoxyribose backbone of each opposed strand to give carbon-centered radicals that, in turn, (4) scavenge dissolved oxygen to initiate a cascade of reactions leading ultimately to the observed cleavages. In this paper we present solution NMR studies that demonstrate for the first time the existence of intermediate **2** and provide an estimate of its lifetime at physiological temperature. These findings permit formulation of an overall kinetic scheme for the reaction of calicheamicin with DNA that frames specific questions about the relative importance of kinetic and thermodynamic factors in the sequence selectivity of its cleavages.

Variable-temperature NMR experiments were undertaken to examine the behavior of the proposed intermediates between **1** and **4**. Methyl thioglycolate (8 equiv, 14 mM) and triethylamine (5 equiv) were added to a methanol-*d*<sub>4</sub><sup>7</sup> solution of calicheamicin  $\gamma_1^1$  (1.6 mM) at -72 °C. Despite the deceptively simple pseudo-first-order disappearance of the methyl trisulfide resonance at  $\delta$  2.50 ( $k_{\text{obsd}} = 2 \times 10^{-4} \text{ s}^{-1}$ ), the sulfur chemistry that occurred was obviously complex. The appearance of multiple signals for H-4, H-5, and H-8 indicated the presence of a variety of calicheamicin-derived species, while in the upfield region of the NMR spectrum, several methylthio-containing compounds were visible, which equilibrated to the methyl disulfide of methyl thioglycolate (RSSCH<sub>3</sub>,  $\delta$  2.44).<sup>8</sup> This reaction manifold was monitored further

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