Entering the leinamycin rearrangement *via* 2-(trimethylsilyl)ethyl sulfoxides

Kripa Keerthi and Kent S. Gates*

Received 25th January 2007, Accepted 7th March 2007
First published as an Advance Article on the web 13th April 2007
DOI: 10.1039/b701179b

Attack of cellular thiols on the antitumor natural product leinamycin is believed to generate a sulfenate intermediate that undergoes subsequent rearrangement to a DNA-alkylating episulfonium ion. Here, 2-(trimethylsilyl)ethyl sulfoxides were employed in a fluoride-triggered generation of sulfenate anions related to the putative leinamycin-sulfenate. The resulting sulfenates enter smoothly into a leinamycin-type rearrangement reaction to afford an episulfonium ion alkylating agent. The results provide evidence that the sulfenate ion is, indeed, a competent intermediate in the leinamycin rearrangement. Further, the molecules examined here may provide a foundation for the design of functional leinamycin analogues that bypass the unstable and synthetically challenging 1,2-dithiolan-3-one 1-oxide moiety found in the natural product.

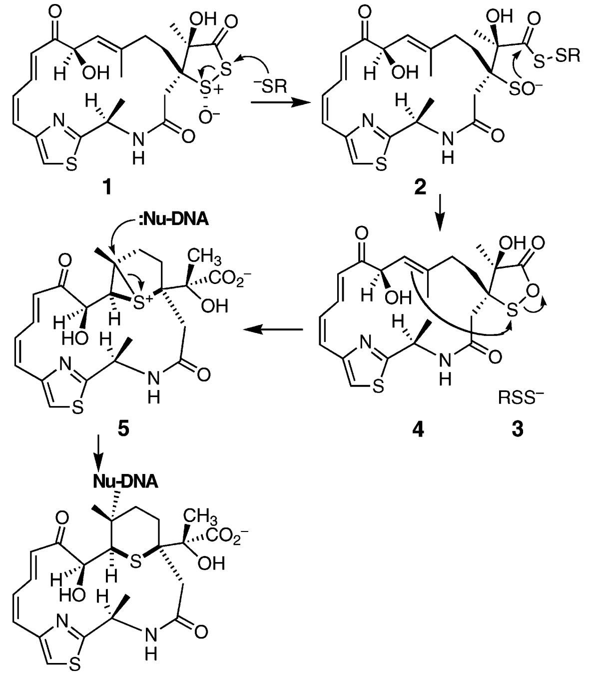
Introduction

Historically, natural products have represented a rich source of structurally novel organic molecules that generate DNA-damaging reactive intermediates *via* interesting and unexpected chemical reactions.[1,2] The characterization of new chemical reactions by which small molecules can modify cellular DNA is relevant to diverse fields including medicinal chemistry, toxicology, and biotechnology.

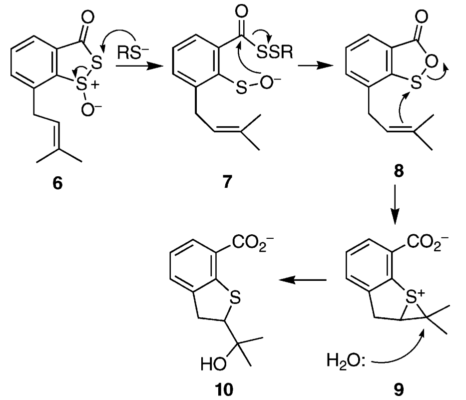
Leinamycin (**1**) provides an interesting example of a structurally unique natural product that damages DNA *via* novel chemical mechanisms.[3–6] Initial attack of cellular thiols on leinamycin's 1,2-dithiolan-3-one 1-oxide "triggering unit" is believed to yield a key sulfenate intermediate (**2**) that undergoes intramolecular cyclization with the neighboring carbonyl group.[7,8] The persulfide (**3**, RSS⁻) ejected in this reaction causes oxidative stress,[9–13] while the resulting 1-oxa-2-thiolan-5-one derivative of leinamycin (**4**) undergoes further rearrangement to yield an episulfonium ion (**5**) that alkylates guanine residues in duplex DNA (Scheme 1).[8–14]

The sulfenate ion (**2**) is proposed[7,8] to be a key intermediate in the thiol-triggered conversion of leinamycin to a DNA-alkylating episulfonium ion, however, to date, there is no experimental support for the existence of this entity. In an effort to fill this gap in our knowledge, we set out to generate discrete sulfenate ions related to **2** and determine whether these intermediates are, in fact, competent to enter the leinamycin rearrangement reaction manifold. For this task, we employed small synthetic molecules containing just the "core" functional groups involved in the leinamycin rearrangement. This approach builds upon our recent finding[15] that stripped-down leinamycin analogues such as **6** smoothly undergo a thiol-triggered, leinamycin-type rearrangement to generate the episulfonium alkylating agent **9** (Scheme 2).

Sulfenate ions (RSO^-) and sulfenic acids (RSOH) are typically not stable, isolable species,[16–18] however, methods exist for their *in situ* generation.[16,19–28] In the present study, we employed the 2-(trimethylsilyl)ethyl sulfoxide group as a sulfenate precursor.



Scheme 1 DNA alkylation by leinamycin (**1**).



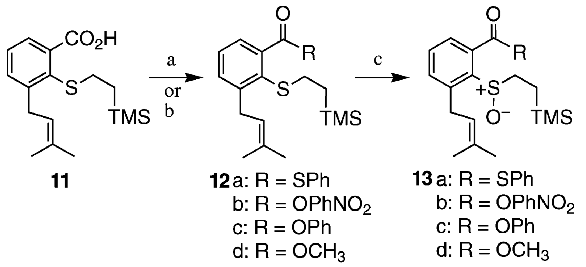
Scheme 2 A small model compound that mimics leinamycin (ref. 15).

Departments of Chemistry and Biochemistry, University of Missouri–Columbia, Columbia, MO 65211, USA. E-mail: gatesk@missouri.edu; Fax: +1 573 882-2754; Tel: +1 573 882-6763

2-(Trimethylsilyl)ethyl sulfoxides can undergo both fluoride-triggered and spontaneous elimination of sulfenate species.[29] For ease of synthesis, we targeted sulfenates containing a neighboring phenyl thioester group in place of the acyl persulfide moiety found in the putative intermediates **2** and **7** (Schemes 1 and 2). Importantly, the leaving group ability of the PhS$^-$ group is similar to that expected for RSS$^-$, as judged by the pK_a values of the conjugate acids.[30,31]

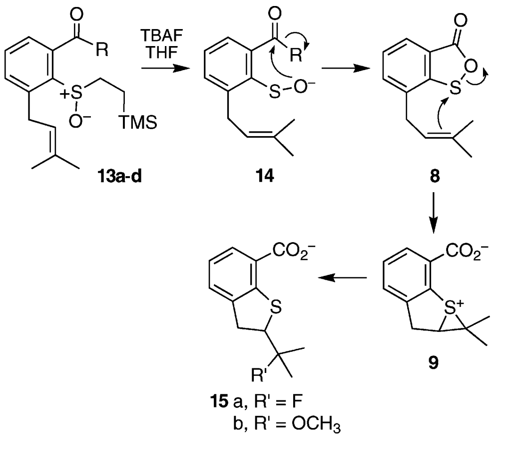
Results and discussion

The sulfenate precursors were prepared as shown in Scheme 3. The known[15] carboxylic acid **11**was activated with DCC–DMAP and converted to the thioester **12a**by reaction with thiophenol. In addition, we prepared ester derivatives **12b** and **c**by analogous reactions. The methyl ester **12d**was synthesized by treatment of **11** with diazomethane. The desired sulfenate precursors **13**were then obtained *via* oxidation of the sulfide group in **12** with dimethyl dioxirane (DMD).[32]



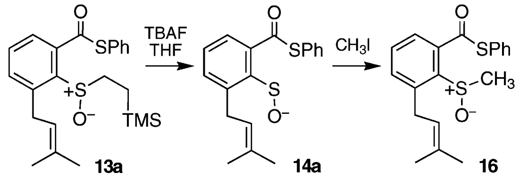
Scheme 3 Preparation of sulfenate precursors **13**. *Reagents and conditions*: a. DCC, DMAP, PhSH or p-NO_2PhOH, or PhOH (for **12a–c**); b. CH_2N_2 (for **12d**); c. DMD, acetone.

Treatment of the thioester **13a** with tetrabutylammonium fluoride (TBAF) in THF rapidly (3 h) affords the rearrangement product **15a** (65%, Scheme 4). This product is envisioned to arise from reaction of the episulfonium ion **9**with excess fluoride ion. When the TBAF-triggered reaction is carried out in a 4 : 1 mixture of THF and methanol, the product (**15b**) resulting from trapping of the episulfonium ion (**9**) with methanol is obtained in 22% yield alongside **15a** (45%). The acids were characterized as the methyl ester derivatives obtained following treatment of the products with diazomethane.



Scheme 4 Fluoride-triggered rearrangement of sulfenate precursors **13**.

Consistent with the expectation that this process proceeds *via* the desired sulfenate ion **14a**, when the reaction is conducted in the presence of excess methyl iodide, the characteristic[16,33] sulfenate trapping product **16**is obtained in 35% yield along with **15a** (25%, Scheme 5). In the context of this reaction, it is useful to note that sulfenate ions are ambident nucleophiles that can react at either sulfur or oxygen.[33] In the leinamycin rearrangement, the oxygen atom of the sulfenate is the nucleophile, whereas the sulfur atom serves as a nucleophile in typical reactions of this functional group with methyl iodide and other alkyl halides.[16,33,34]

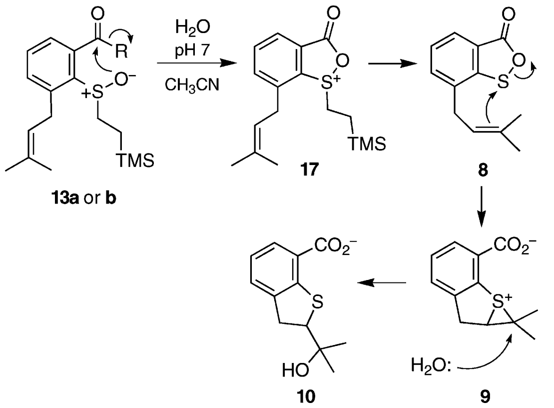


Scheme 5 Trapping the sulfenate intermediate.

The ester derivatives (**13b–d**) also undergo fluoride-triggered rearrangement in THF to provide **15a** in yields comparable to those obtained from **13a**. Evidently, a good leaving group (*e.g.* PhS$^-$ or p-NO_2PhO^-) on the carbonyl is not required for the rearrangement to proceed. The cyclization of **14** to **8** may be favored by the potent nucleophilicity of the sulfenate anion.[35]

Extended incubation of **13a** for 20 h in THF–MeOH in the *absence* of TBAF does not afford any rearranged product **15b**, yielding instead only the product **13d** resulting from methanolysis of the thioester group in the starting material. However, in a different solvent mixture consisting of 1 : 1 CH_3CN and sodium phosphate buffer (50 mM, pH 7), compounds **13a** and **13b** undergo a slow (48 h), fluoride-*independent* conversion to the episulfonium-derived product **10**, albeit in somewhat lower yields (30%) than those obtained in the fluoride-triggered process.[36]

Initially, we suspected that this fluoride-independent reaction might proceed *via* the same sulfenate intermediate (**14**, Scheme 4) generated in the fluoride-triggered reactions, because it is known that 2-(trimethylsilyl)ethyl sulfoxides can undergo fluoride-independent release of sulfenate species.[29] However, the intermediacy of a free sulfenate anion or sulfenic acid in these reactions was called into question by our inability to trap this intermediate with methyl iodide under our standard trapping conditions used previously.[34] Further evidence arguing against a straightforward elimination of sulfenate from **13a** and **13b** in this fluoride-independent process was provided by the observation that the reaction occurs only with these activated esters. The less reactive esters **13c** and **13d**return starting material under these reaction conditions. Thus, the 2-(trimethylsilyl)ethyl sulfoxide group is inherently stable in the context of **13c** and **13d**; however, interaction of this functional group with the adjacent activated ester groups in **13a** and **13b** stimulates rearrangement to **10**. This transformation may proceed *via* initial attack of the sulfoxide oxygen on the adjacent activated carbonyl group to yield **17**, followed by loss of the 2-(trimethylsilyl)ethyl group to generate the oxathiolanone intermediate **8** that, in turn, yields the episulfonium ion **9** (Scheme 6).[37]



Scheme 6 Proposed mechanism for fluoride-independent conversion of **13a** and **13b** to **10**.

Conclusions

In summary, we utilized 2-(trimethylsilyl)ethyl sulfoxides as precursors in the fluoride-triggered generation of sulfenate ions related to a key intermediate (**2**) proposed previously in the thiol-triggered alkylation of DNA by leinamycin (Scheme 1). Our results provide evidence that the sulfenate ion is, indeed, a competent intermediate in the leinamycin rearrangement reaction. In addition, for two of the 2-(trimethylsilyl)ethyl sulfoxides (**13a** and **b**), we observed an unexpected fluoride-independent reaction in which attack of the sulfoxide group on a neighboring activated ester, followed by loss of the 2-(trimethylsilyl)ethyl group, affords entry into the leinamycin rearrangement *via* the oxathiolanone intermediate **8**. Overall, these studies provide a better grasp of the intermediates involved in the thiol-triggered conversion of leinamycin to a DNA-alkylating agent. In addition, the molecules examined here may provide a foundation for the design of functional leinamycin analogues that bypass the unstable[38] and synthetically challenging[39,40] 1,2-dithiolan-3-one 1-oxide moiety found in the natural product.

Experimental

Materials were purchased from the following suppliers: HPLC grade solvents, Fisher; silica gel 60 (0.04–0.063 mm pore size) for column chromatography, Merck; TLC plates coated with general purpose silica containing UV$_{254}$ fluorophore, Aldrich Chemical Company; all chemicals were purchased from Aldrich Chemical Company and were of the highest purity available unless otherwise noted. Water was distilled, deionized and glass redistilled. All reactions were carried out under an atmosphere of nitrogen, unless otherwise noted.

3-(3-Methylbut-2-enyl)-2-[2-(trimethylsilanyl)-ethylsulfanyl]-benzoic acid *S*-phenyl ester 12a

To a solution of **11**[15] (200 mg, 0.62 mmol) in dry THF (2 mL) maintained under an atmosphere of nitrogen, dicyclohexyl carbodiimide (153 mg, 0.74 mmol) and a catalytic amount of 4-dimethylaminopyridine (7.6 mg, 0.06 mmol) were added. The solution was allowed to stir for 30 min and thiophenol (76 μL, 0.74 mmol) was added. The resulting mixture was stirred at 24 °C for 48 h. The dicyclohexylurea precipitate was filtered off and the solvent was evaporated under reduced pressure to yield a yellow oil. The crude product was purified by flash column chromatography on silica gel eluted with 19 : 1 hexane : ethylacetate to yield **12a** as a colorless oil (211 mg, 82%, $R_f = 0.5$ in 10 : 1 hexane : ethylacetate). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.60–7.28 (m, 8H, aromatic), 5.28 (m, 1H), 3.72 (d, J = 7.1 Hz, 2H), 2.85 (m, 2H), 1.77 (s, 6H), 0.87 (m, 2H), 0.0 (s, 9H) ppm. ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ 193.05, 147.58, 145.64, 134.47, 133.12, 131.49, 130.80, 129.43, 129.24, 128.39, 125.02, 122.78, 33.9, 32.78, 25.77, 18.03, 17.56, −1.80 ppm. HRMS (ESI) calcd for $C_{23}H_{30}OS_2SiNa$ $[M + Na]^+$ 437.1399, found 437.1419.

3-(3-Methylbut-2-enyl)-2-[2-(trimethylsilanyl)-ethylsulfanyl]-benzoic acid *p*-nitrophenyl ester 12b

To a stirred solution of **11**[15] (200 mg, 0.62 mmol) in dry, distilled THF (2 mL) under nitrogen, dicyclohexyl carbodiimide (153 mg, 0.74 mmol) and a catalytic amount of 4-dimethylaminopyridine (7.6 mg, 0.06 mmol) were added. After about 30 min of stirring, *p*-nitrophenol (103 mg, 0.74 mmol) in THF (1 mL) was added and stirring was continued for 48 h. The dicyclohexylurea precipitate was removed by filtration and the filtrate was evaporated under reduced pressure to give a dark yellow oil. Flash column chromatography on silica gel eluted with 19 : 1 hexane : ethylacetate gave **12b** as a pale yellow oil (247 mg, 90% yield, $R_f = 0.55$ in 10 : 1 hexane : ethylacetate). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.38 (d, J = 7.0 Hz, 2H), 7.57–7.44 (m, 5H), 5.35 (m, 1H), 3.78 (d, J = 7.1 Hz, 2H), 2.89 (m, 2H), 1.82 (s, 6H), 0.87 (m, 2H), 0.0 (s, 9H) ppm. ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ 166.39, 155.75, 147.78, 145.43, 138.38, 133.36, 132.27, 128.68, 126.04, 125.28, 122.61, 122.47, 33.51, 32.78, 25.76, 18.03, 17.52, −1.91 ppm. HRMS (ESI) calcd for $C_{23}H_{29}NO_4SSiNa$ $[M + Na]^+$ 466.1478, found 466.1490.

3-(3-Methylbut-2-enyl)-2-[2-(trimethylsilanyl)-ethylsulfanyl]-benzoic acid phenyl ester 12c

To a stirred solution of **11**[15] (200 mg, 0.62 mmol) in dry, distilled THF (2 mL) under nitrogen, dicyclohexyl carbodiimide (153 mg, 0.74 mmol) and a catalytic amount of 4-dimethylaminopyridine (7.6 mg, 0.06 mmol) were added. After about 30 min of stirring, phenol (69.64 mg, 0.74 mmol) in dry THF (1 mL) was added and stirring was continued for 48 h. At the end of the reaction, the dicyclohexylurea precipitate was removed by filtration and the filtrate was evaporated under reduced pressure to give a pale yellow oil. Flash column chromatography on silica gel eluted with 19 : 1 hexane : ethylacetate gave **12c** as a colorless oil (187 mg, 76% yield, $R_f = 0.51$ in 10 : 1 hexane : ethylacetate). ^{1}H-NMR (250 MHz, $CDCl_3$) δ 7.50–7.31 (m, 8H, aromatic), 5.34 (m, 1H), 3.80 (d, J = 7.1 Hz, 2H), 2.91 (m, 2H), 1.82 (s, 6H), 0.90 (m, 2H), 0.0 (s, 9H) ppm. ^{13}C-NMR (62.9 MHz, $CDCl_3$) δ 167.47, 151.02, 147.49, 139.44, 133.09, 132.09, 131.65, 129.47, 128.51, 125.96, 122.85, 121.58, 33.42, 32.86, 25.76, 18.03, 17.49, −1.90 ppm. HRMS (ESI) calcd for $C_{23}H_{30}O_2SSiNa$ $[M + Na]^+$ 421.1627, found 421.1637.

3-(3-Methylbut-2-enyl)-2-[2-(trimethylsilanyl)-ethylsulfanyl]-benzoic acid methyl ester 12d

To a solution of **11**[15] (50 mg, 0.15 mmol) in ether (1 mL) freshly prepared diazomethane (1 mL of a 0.66 M solution in ether, warning: EXPLOSION HAZARD) was added.[41] When the reaction was complete as judged by thin layer chromatography the solvent was evaporated under reduced pressure to give **12d** as a colorless oil (44 mg, 85%, $R_f = 0.68$ in 9 : 1 hexane : ethylacetate) as a pure compound. ^{1}H-NMR (250 MHz, CDCl$_3$) δ 7.32 (m, 3H), 5.27 (m, 1H), 3.93 (s, 3H), 3.70 (d, $J = 7.1$ Hz, 2H), 3.81 (m, 2H), 1.76 (s, 1H), 0.83 (m, 2H), 0.0 (s, 9H) ppm. ^{13}C-NMR (62.9 MHz, CDCl$_3$) δ 169.58, 147.14, 139.97, 132.95, 131.85, 131.20, 128.28, 125.71, 122.91, 52.29, 33.23, 32.94, 25.75, 18.01, 17.48, −1.86 ppm. HRMS (ESI) calcd for $C_{18}H_{28}O_2SSiNa$ $[M + Na]^+$ 359.1471, found 359.1460.

General procedure for the conversion of sulfides 12a–d to sulfoxides 13a–d

To a rapidly stirred dilute solution of the sulfide **12a–d** (50 mg, 0.12 mmol) in HPLC grade acetone (10 mL) freshly prepared dimethyl dioxirane[32] (1.5 mL of a ~ 0.09 M solution in acetone) was added slowly. The reaction was fast and careful monitoring by TLC was essential to limit overoxidation. The solvent mixture was evaporated under reduced pressure to give the sulfoxide **13a–d** as a colorless oil and as a pure compound. These compounds are unstable and were used without further purification.

3-(3-Methylbut-2-enyl)-2-[2-(trimethylsilanyl)-ethanesulfinyl]-benzoic acid *S*-phenyl ester 13a

Obtained in 72% yield ($R_f = 0.56$ in 4 : 1 hexane : ethylacetate). ^{1}H-NMR (250 MHz, CDCl$_3$) δ 7.59–7.55 (m, 3H), 7.48–7.41 (m, 5H), 5.22 (m, 1H), 3.79 (m, 2H), 3.34 (m, 1H), 2.98 (m, 1H), 1.73 (s, 6H), 1.22 (m, 1H), 0.78 (m, 1H), 0.03 (s, 9H) ppm. ^{13}C-NMR (62.9 MHz, CDCl$_3$) δ 192.09, 143.16, 140.14, 138.78, 134.61, 133.79, 130.29, 129.59, 129.27, 127.79, 126.38, 122.25, 50.86, 30.37, 25.69, 18.13, 10.89, −1.90 ppm. LRMS (ESI) calcd for $C_{23}H_{31}O_2S_2Si$ $[M + H]^+$ 431.15, found 431.12.

3-(3-Methylbut-2-enyl)-2-[2-(trimethylsilanyl)-ethanesulfinyl]-benzoic acid *p*-nitrophenyl ester 13b

Obtained in 85% yield ($R_f = 0.27$ in 5 : 1 hexane : ethylacetate). ^{1}H-NMR (300 MHz, CDCl$_3$) δ 8.34 (d, $J = 2.2$ Hz, 2H), 7.63–7.29 (m, 5H), 5.22 (m, 1H), 3.55 (d, $J = 6.8$ Hz, 2H), 3.48 (m, 1H), 2.95 (m, 1H), 1.78 (s, 6H), 1.24 (m, 1H), 0.87 (m, 1H), 0.0 (s, 9H) ppm. LRMS (ESI) calcd for $C_{23}H_{30}NO_5SSi$ $[M + H]^+$ 460.16, found 460.19.

3-(3-Methylbut-2-enyl)-2-[2-(trimethylsilanyl)-ethanesulfinyl]-benzoic acid phenyl ester 13c

Obtained in 96% yield ($R_f = 0.32$ in 5 : 1 hexane : ethylacetate). ^{1}H-NMR (250 MHz, CDCl$_3$) δ 7.64–7.29 (m, 8H, aromatic), 5.23 (m, 1H), 3.66 (d, $J = 6.7$ Hz, 2H), 3.49 (m, 1H), 2.99 (m, 1H), 1.76 (s, 6H), 1.27 (m, 1H), 0.84 (m, 1H), 0.02 (s, 9H) ppm. ^{13}C-NMR (62.9 MHz, CDCl$_3$) δ 166.61, 150.74, 141.52, 133.95, 133.04, 131.78, 130.48, 129.46, 127.99, 126.01, 122.05, 121.71, 50.11, 33.87, 32.13, 31.55, 18.14, 11.14, −1.99 ppm. HRMS (ESI) calcd for $C_{23}H_{30}O_3SSiNa$ $[M + Na]^+$ 437.1577, found 437.1564.

3-(3-Methylbut-2-enyl)-2-[2-(trimethylsilanyl)-ethanesulfinyl]-phenyl]benzoic acid methyl ester 13d

Obtained in 53% yield ($R_f = 0.38$ in 5 : 1 hexane : ethylacetate). ^{1}H-NMR (250 MHz, CDCl$_3$) δ 7.40–7.28 (m, 3H), 5.14 (m, 1H), 3.84 (s, 3H), 3.60 (d, $J = 6.7$ Hz, 2H), 3.39 (m, 1H), 2.90 (m, 1H), 1.67 (s, 6H), 1.22 (m, 1H), 0.79 (m, 1H), 0.0 (s, 9H) ppm. ^{13}C-NMR (62.9 MHz, CDCl$_3$) δ 168.45, 141.83, 141.16, 133.73, 132.82, 132.25, 130.33, 127.58, 122.25, 52.63, 50.20, 30.67, 25.70, 18.12, 11.22, −1.91 ppm. HRMS (ESI) calcd for $C_{18}H_{28}O_3SSiNa$ $[M + Na]^+$ 375.1420, found 375.1428.

Fluoride-triggered production of 2-(1-fluoro-1-methylethyl)-2,3-dihydrobenzo[*b*]thiophene-7-carboxylic acid methyl ester (15a) by treatment of (13a–d) with tetrabutylammonium fluoride in THF, followed by diazomethane workup

A solution of **13a** (20 mg, 0.046 mmol) in THF (1 mL) was placed in a flame-dried flask flushed with nitrogen. To this solution, tetrabutylammonium fluoride (0.37 mL of a 1 M solution in THF, 0.37 mmol, 0.27 M) from a freshly opened bottle was added. The reaction mixture turned deep yellow and was stirred for 3 h. Dilute HCl (1 mL of a 1 M solution, pH ≈ 3) was added, followed by addition of diazomethane (2 mL of a 0.66 M solution in ether, warning: EXPLOSION HAZARD) with vigorous stirring. Stirring was continued for 30 min and the mixture was extracted with diethyl ether (3 × 5 mL). The ether extracts were combined and washed with water (1 × 5 mL) followed by brine (1 × 5 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield a pale yellow oil. Flash column chromatography on silica gel eluted with 9 : 1 hexane : ethylacetate gave **15a** as a colorless oil (7.7 mg, 65%, $R_f = 0.42$ in 6 : 1 hexane : ethylacetate). ^{1}H-NMR (500 MHz, d^6-acetone) δ 7.78 (dd, $J = 8$, 1 Hz, 1 H), 7.41 (qd, $J = 8$, 1 Hz, 1 H), 7.12 (t, $J = 7.5$ Hz, 1 H), 4.06 (ddd, $J = 12$, 9.5, 6.5 Hz, 1 H), 3.86 (s, 3 H), 3.46 (dd, $J = 16.5$, 9.5 Hz, 1 H), 3.36 (dd, $J = 16.5$, 6.5 Hz, 1 H), 1.42 (d, $J = 21.5$, 3 H), 1.37 (d, $J = 21.5$ Hz, 3 H) ppm. ^{19}F-NMR (235.35 MHz, CDCl$_3$) δ −139.35 (complex m) ppm. (^{19}F NMR chemical shift was determined relative to internal CFCl$_3$ at δ 0.0). ^{13}C-NMR (125.75 MHz, CDCl$_3$) δ 166.67, 145.14, 141.32, 128.90, 127.79, 124.19, 123.63, 96.95 (d, $J = 169.8$ Hz), 55.88 (d, $J = 25.2$ Hz), 52.16, 36.29 (d, $J = 3.8$ Hz), 25.48 (d, $J = 23.9$ Hz), 22.74 (d, $J = 23.9$ Hz) ppm. HRMS (EI) calcd for $C_{13}H_{15}FO_2S$ $[M^+]$ 254.0776, found 254.0781. Similarly, compounds **13b–d** generate **15a** in comparable yields (**13b**, 50%; **13c**, 56%; **13d**, 54%).

Generation of 2-(1-methoxy-1-methylethyl)-2,3-dihydrobenzo-[*b*]thiophene-7-carboxylic acid methyl ester 15b by treatment of 13a with tetrabutylammonium fluoride in THF–MeOH, followed by diazomethane workup

To a solution of **13a** (20 mg, 0.046 mmol) in THF (0.8 mL) under nitrogen, dry distilled methanol (200 μL) was added followed by tetrabutylammonium fluoride (0.37 mL of a 1 M solution in THF, 0.37 mmol, 0.27 M). The reaction mixture turned dark yellow and was stirred for 3 h. Dilute HCl (1 mL of a 1 M solution, pH ≈ 3) was added and the resulting biphasic mixture was treated with diazomethane (2 mL of a ~ 0.66 M solution in ether, warning: EXPLOSION HAZARD) with vigorous stirring. After 30 min, the mixture was extracted with diethyl ether (3 × 5 mL). The ether extracts were combined, washed with water (1 × 5 mL) followed by brine (1 × 5 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield a pale yellow oil. Flash column chromatography on silica gel eluted with 6 : 1 hexane : ethylacetate gave **15a** (5.3 mg, 45%) as a colorless oil and **15b** (2.7 mg, 22%, $R_f = 0.33$ in 6 : 1 hexane : ethylacetate) as a colorless oil. All spectral data for this compound matched those reported previously.[15]

Trapping by methyl iodide of the sulfenate intermediate 14a generated from 13a

To a stirred solution of **13a** (20 mg, 0.046 mmol) in THF (1 mL) under nitrogen, tetrabutylammonium fluoride (0.37 mL of a 1 M solution in THF, 0.37 mmol, 0.27 M), and excess methyl iodide (0.14 mL, 2.3 mmol, for a final concentration of 1.7 M) were added. The reaction was stirred for 3 h and quenched by dilute HCl (1 mL of a 1 M solution, pH ≈ 3). To this biphasic reaction mixture, diazomethane (2 mL of a ~0.66 M solution in ether, warning: EXPLOSION HAZARD) was added with vigorous stirring. After 30 min, the mixture was extracted with diethyl ether (3 × 5 mL). The combined ether extracts were washed with water (1 × 5 mL) followed by brine (1 × 5 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure. Flash column chromatography on silica gel eluted with 4 : 1 hexane : ethylacetate yielded **15a** (3 mg, 25%) and **16** (4.3 mg, 35%, $R_f = 0.09$ in 4 : 1 hexane : ethylacetate). ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.46 (d, $J = 3.75$ Hz, 1 H), 7.42 (t, $J = 3.75$ Hz, 1 H), 7.37 (d, $J = 3.75$ Hz), 5.20 (m, 1 H), 3.93 (s, 3 H), 3.68 (d, $J = 3.5$ Hz, 2 H), 3.05 (s, 3 H), 1.74 (d, $J = 5.5$ Hz, 6 H) ppm. ^{13}C-NMR (125.75 MHz, $CDCl_3$) δ 168.34, 141.87, 141.40, 133.93, 132.92, 131.87, 130.45, 127.58, 121.93, 52.65, 40.17, 30.37, 25.62, 18.05 ppm. HRMS (EI) calcd for $C_{14}H_{18}O_3S$ [M $^+$] 266.0976, found 266.0973.

Fluoride-independent conversion of 13a and 13b in aqueous buffer followed by diazomethane workup to yield 2-(1-hydroxy-1-methylethyl)-2,3-dihydrobenzo[*b*]thiophene-7-carboxylic acid methyl ester (10) in acetonitrile–aqueous buffer

Compound **13a** (20 mg, 0.046 mmol) was stirred in a solution of acetonitrile (2.5 mL), sodium phosphate buffer (0.5 mL of a 500 mM, pH 7), and water (2 mL). Final concentrations in the reaction mixture were: **13a**, 9.2 mM, sodium phosphate, 50 mM, pH 7, acetonitrile 50% by volume. Dilute HCl (1 mL of a 1 M solution, pH ≈ 3) was added to the reaction, followed by diazomethane (2 mL of a ~0.66 M solution in ether, warning: EXPLOSION HAZARD). The mixture was stirred for 30 min and then extracted with diethyl ether (3 × 5 mL). The combined ether extracts were washed with water (1 × 5 mL) and brine (1 × 5 mL), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to yield a pale yellow oil. Flash column chromatography on silica gel eluted with 6 : 1 hexane : ethylacetate yielded **10** as a colorless oil (3.9 mg, 33%, $R_f = 0.15$ in 6 : 1 hexane : ethylacetate). All spectral data for this compound matched those reported previously. Similarly, **13b** affords **10** (32% yield) under these reaction conditions. It is noteworthy that addition of KF (50 mM) does not alter the rate or yield of this reaction. Finally, compounds **13c** and **13d** remained unchanged when subjected to the conditions described above (either with or without KF).

Acknowledgements

We thank the National Institutes of Health (CA 83925 and CA 119131) for support of this research.

Notes and references

1 K. S. Gates, in *Comprehensive Natural Products Chemistry*, ed. E. T. Kool, Pergamon, New York, 1999, vol. 7, pp. 491–552.
2 W. C. Tse and D. L. Boger, *Chem. Biol.*, 2004, **11**, 1607–1617.
3 K. S. Gates, *Chem. Res. Toxicol.*, 2000, **13**, 953–956.
4 M. Hara, K. Asano, I. Kawamoto, T. Takiguchi, S. Katsumata, K.-I. Takahashi and H. Nakano, *J. Antibiot.*, 1989, **42**, 1768–1774.
5 M. Hara, Y. Saitoh and H. Nakano, *Biochemistry*, 1990, **29**, 5676–5681.
6 M. Hara, I. Takahashi, M. Yoshida, I. Kawamoto, M. Morimoto and H. Nakano, *J. Antibiot.*, 1989, **42**, 333–335.
7 S. B. Behroozi, W. Kim and K. S. Gates, *J. Org. Chem.*, 1995, **60**, 3964–3966.
8 A. Asai, M. Hara, S. Kakita, Y. Kanda, M. Yoshida, H. Saito and Y. Saitoh, *J. Am. Chem. Soc.*, 1996, **118**, 6802–6803.
9 S. J. Behroozi, W. Kim, J. Dannaldson and K. S. Gates, *Biochemistry*, 1996, **35**, 1768–1774.
10 K. Mitra, W. Kim, J. S. Daniels and K. S. Gates, *J. Am. Chem. Soc.*, 1997, **119**, 11691–11692.
11 T. Chatterji and K. S. Gates, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 535–538.
12 T. Chatterji and K. S. Gates, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 1349–1352.
13 T. Chatterji, K. Keerthi and K. S. Gates, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 3921–3924.
14 H. Zang and K. S. Gates, *Chem. Res. Toxicol.*, 2003, **16**, 1539–1546.
15 T. Chatterji, M. Kizil, K. Keerthi, G. Chowdhury, T. Posposil and K. S. Gates, *J. Am. Chem. Soc.*, 2003, **125**, 4996–4997.
16 J. S. O'Donnell and A. L. Schwan, *J. Sulfur Chem.*, 2004, **25**, 183–211.
17 K. Goto, M. Holler and R. Okazaki, *J. Am. Chem. Soc.*, 1997, **119**, 1460–1461.
18 T. Okuyama, K. Miyake, T. Fueno, T. Yoshimura, S. Soga and E. Tsukurimichi, *Heteroat. Chem.*, 1992, **3**, 577–583.
19 H. Adams, J. C. Anderson, R. Bell, D. N. Jones, M. R. Peel and N. C. O. Tomkinson, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3967–3973.
20 M. Hashmi, S. Vamvakas and M. W. Anders, *Chem. Res. Toxicol.*, 1992, **5**, 360–365.
21 E. Block, *Angew. Chem., Int. Ed. Engl.*, 1992, **31**, 1135–1178.
22 J. W. Cubbage, Y. Guo, R. D. McCulla and W. S. Jenks, *J. Org. Chem.*, 2001, **66**, 8722–8736.
23 F. Nagatsugi, T. Kawasaki, D. Usui, M. Maeda and S. Sasaki, *J. Am. Chem. Soc.*, 1999, **121**, 6753–6754.
24 A. R. Katritzky, I. Takahashi and C. M. Marson, *J. Org. Chem.*, 1986, **51**, 4914–4920.
25 C. Caupene, C. Boudou, S. Perrio and P. Metzner, *J. Org. Chem.*, 2005, **70**, 2812–2815.
26 M. C. Aversa, A. Barattucci, P. Bonaccorsi and P. Giannetto, *J. Org. Chem.*, 2005, **70**, 1986–1992.
27 P. Rose, M. Whiteman, P. K. Moore and Y. Z. Zhu, *Nat. Prod. Rep.*, 2005, **22**, 351–368; R. Kubec, S. Kim, D. M. McKeon and R. A. Musah, *J. Nat. Prod.*, 2002, **65**, 960–964.
28 J. S. O'Donnell and A. L. Schwan, *Tetrahedron Lett.*, 2003, **44**, 6293–6296.
29 S. Chambert, J. Desire and J.-L. Decout, *Synthesis*, 2002, 2319–2334.
30 S. A. Everett, L. K. Folkes and P. Wardman, *Free Radical Res.*, 1994, **20**, 387–400.
31 A. H. Otto and R. Steudel, *Eur. J. Inorg. Chem.*, 1999, 2057–2061.
32 W. Adam, J. Bialas and L. Hadjiarapoglou, *Chem. Ber.*, 1991, **124**, 2377.
33 D. R. Hogg and A. Robertson, *Tetrahedron Lett.*, 1974, **15**, 3783–3784.
34 Sulfenic acids (RSOH) can also act as electrophiles that are susceptible to nucleophilic attack at the sulfur atom. See reference 17 and: S. Sivaramakrishnan, K. Keerthi and K. S. Gates, *J. Am. Chem. Soc.*, 2005, **127**, 10830–10831.
35 For a related example involving intramolecular attack of an α-effect nucleophile, hydroxylamine (RNHOH), on a methyl ester,

see: B. G. Cox, D. M. A. Grieve and A. E. A. Porter, *J. Chem. Soc., Perkin Trans. 2*, 1975, 1512–1515.

36 Added KF has no effect on either the rates or yields of these reactions, presumably because hydration of the fluoride ion in aqueous solution diminishes the rate of its reaction with the 2-(trimethylsilyl)ethyl group. For example, see: R. I. Hogrefe, A. P. McCaffrey, L. U. Borozdina, E. S. McCampbell and M. M. Vaghefi, *Nucleic Acids Res.*, 1993, **21**(20), 4739–4741.

37 In a related reaction, removal of a 2-(trimethylsilyl)ethyl protecting group from sulfur can be stimulated by acylating agents, see: Y. Wang, M. Koreeda, T. Chatterji and K. S. Gates, *J. Org. Chem.*, 1998, **63**, 8644–8645.

38 Y. Kanda, T. Ashizawa, S. Kakita, Y. Takahashi, M. Kono, M. Yoshida, Y. Saitoh and M. Okabe, *J. Med. Chem.*, 1999, **42**, 1330–1332.

39 Y. Kanda and T. Fukuyama, *J. Am. Chem. Soc.*, 1993, **115**, 8451–8452.

40 G. Pattenden and A. J. Shuker, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1215–1221.

41 Aldrich Technical Bulletin AL-180 (http://www.sigmaaldrich.com/aldrich/bulletin/al_techbull_al180.pdf).